Medical Library

BULLETIN

OF THE

JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

Vol. XLVII, No. 6 DECEMBER, 1930

Contents

Amyotonia Congenita (Oppenheim's Disease) in Identical Twins. WILEY D. FORBUS AND FRED S. WOLF..... 309

Practical Conclusions Drawn from One Thousand Forcep Deliveries. H. J. STANDER, M.D..... 323

The Pathogenesis of the Forms of Jaundice. ARNOLD RICE RICH..... 338

Cervical Adenitis Due to Bacillus Fusiformis. W. M. FIROR..... 378

Acetone Bodies in Normal Pregnancy and in the Toxemias of Pregnancy. H. J. STANDER AND J. F. CADDEN..... 382

Programs of the Medical Research Society, 1929–1930..... 391

Index..... 393

PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS

BALTIMORE, MARYLAND

Made in United States of America

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorised on July 3, 1918.

3 IMPORTANT AIDS TO PHYSICIANS AND SURGEONS

For Respiratory Diseases

DISULPHAMIN

Orto-oxibenzoyl-sulphon-nucleino-formol-sodium-tetradimethylamino-antipyrin-bicamphorated

A Reliable Oxytocic

THYMOPHYSIN

(Tomasulzy)

A Valuable Hemostatic

STRYPHNON

(Meyer & Allbrecht)

Please send literature on items checked:

DISULPHAMIN ☐ THYMOPHYSIN ☐ STRYPHNON ☐

AMERICAN BIO-CHEMICAL LABORATORIES, INC.

235 Fourth Avenue New York City

Sole Agents for Canada NATIONAL DRUG AND CHEMICAL COMPANY *of Canada, Ltd, Montreal*

AMYOTONIA CONGENITA (OPPENHEIM'S DISEASE) IN IDENTICAL TWINS

WILEY D. FORBUS AND FRED S. WOLF

From the Department of Pathology, The Johns Hopkins University, and the Department of Pediatrics, Sinai Hospital, Baltimore, Md.)

Among the very few recorded autopsies on cases of amyotonia congenita there appears to be none in which the disease was found in twins. Recently the opportunity to make complete clinical and pathological studies of identical twins, each suffering from the disease, has presented itself. In spite of the fact that no new pathological findings were made in these studies, they are considered worth recording merely because the appearance of the disease in two children, developing from the same ovum, adds emphasis to the prevalent idea that the disease is one of embryonic rather than post-natal origin.

The entire life histories as well as clinical histories of the two children under discussion were identical. Hence it is that the clinical records which follow form a composite picture of the disease as it appeared in the two subjects. On account of the close uniformity and similarity of findings in the two autopsies, a single composite protocol will likewise suffice.

The information in the clinical history was obtained almost entirely from the father of the children. The mother, a very quiet, retiring person, added only an occasional word. They stated that their own health was excellent. It is interesting to note that the parents were first cousins and that the children were conceived while the father and mother were in their early forties. Seven children were born to them. Of these the first two are living in good health and possess average intelligence; the third was a blue baby that died at the age of three weeks. A miscarriage terminated the fourth pregnancy. Another blue baby resulted from the fifth pregnancy, this one living only three or four weeks. The twins were the result of the sixth pregnancy.

During the pregnancy of which the twins were the outcome, the mother withstood an attack of erysipelas. At term the children were delivered at home without operative interference. The first born

weighed four pounds, thirteen ounces, the second born weighed three pounds and thirteen ounces. The physician who attended the delivery stated that the children were single ovum twins as indicated by the presence of a single placenta. According to the father's story they were properly fed on a carefully balanced diet. There had been difficulty in obtaining bowel movements in these children from their birth. They were never able to sit erect.

Nothing attracted the attention of the father until the children were five months old. At this time it became evident that they were not moving their extremities as the other children had done. Watching them carefully he found that there was great difficulty in suckling due to frequent choking. However, a constant gain in weight was obtained. Never did the twins have the ability to hold their own bottles. Once they succeeded in raising their heads from the pillow only to lose this ability after a brief while. The father thought that fear of him was responsible for a peculiar manner in which they had breathed during the last six months. Before they were six months old he had noticed that their arms and legs could be placed in unusual positions. Difficulty in swallowing was always present, frequently causing them to choke on their own saliva.

In the hospital ward each of them was found to have an elevation of temperature, the maximum in either case being 103°F. They appeared fairly well developed and nourished as they lay upon the back, crying in weak kitten-like sounds with each inspiration. They were perfectly relaxed. The arms and legs were abducted and internally rotated. The legs were fully extended with the toes showing a distinct droop. The most striking of all was the appearance of the thorax and the character of the respirations. The thorax showed the "pigeon-breast" deformity in extreme degree, and there was in addition a marked flare of the lower ribs accompanying a pronounced Harrison's groove. There was no enlargement of the epiphyses of the ribs. Breathing was entirely diaphragmatic, consisting of deep inspiration with accompanying wide excursion of the chest wall outward, followed by quite forceful expiration. In no part of the body was any wasting or loss of tissue noted. The arms and legs were full and round. An ill-defined, irregular, pinkish discoloration was present over the forehead and a small reddish papular eruption over the chest.

The posterior fontanelle was closed; the anterior one measured 3 cm. in transverse diameter. In the chest the signs of a lobular pneumonia were obtained. In the neurological examination was found marked generalized flaccidity of the muscles, absence of all the deep and superficial reflexes, abnormally mobile extremities, no cervical rigidity, negative Kernig, Babinski, Chaddock, and Brudzinski signs, absence of clonus, failure to react to either galvanic or faradic stimuli.

Thorough laboratory examination was possible only in the case of the first of the twins to be admitted to the service. The second one was in the ward only a few hours before death occurred:

Blood Picture:

	1	2
Red blood cells	3,900,000	4,150,000
White blood cells	22,200–23,800	55,300
Haemoglobin (Sahli)	75%	48%
Differential 200 cells		
PMN	65%	64%
PME	1%	1.5%
PMB	0	0
SL	29%	27.5%
LL	1%	3%
Mono	3%	3%
Trans	1%	2%

Urine.....Negative. Negative.

Nose and throat culture.....Negative for diphtheria (both cases).

Vaginal smear.....Negative for Neisser organisms (both cases).

Tuberculin .1 mgm......Negative. Not done.

Blood Wassermann (Ice-box and water-bath) Negative in both cases.

Blood chemistry:

Calcium	11.6 mgm. %	Not done.
Phosphorus	3.86 mgm. %	
Sugar	192.0 mgm. %	
Urea	31.06 mgm. %	
Urea N	14.56 mgm. %	
CO_2 combining power	29.0 Vol. %	

Blood Culture.....Pneumococcus type IV, 25 colonies /cc. Not done.

Spinal fluid.....Globulin, Wassermann, colloidal mastic and colloidal gold curves negative. Not done.

X-ray: Examination of the long bones and the skull negative in both cases. Examination of the chest showed pneumonic consolidation of the right upper and a partial consolidation of the left lung in both cases.

The clinical findings seemed, therefore, to justify the diagnosis of amyotonia congenita, death being due to pneumonia in both cases.

Autopsies No. H-10844 and H-10845.

Anatomical Diagnosis—H-10844:

Amyotonia congenita; deformity of chest. Lobular pneumonia; atelectasis of lungs.

Anatomical Diagnosis—H-10845:

Amyotonia congenita; deformity of chest; lobular pneumonia (Pneumococcus Type IV); malformation of right great toe ("Hammer-toe").

Body: In each subject the body measured 70 cm. in length. The weights were not recorded. No emaciation was present. The size of the arms and the legs was not unusual for the age. All the muscles were quite flaccid, allowing extreme extension of the limbs. The facial features were not such as to lead one to suspect any wasting of the muscles or any other abnormality in the soft tissues. The chest in each subject was strikingly deformed, the deformity consisting of a deep depression or groove extending from the mid-point of the clavicle to the inferior costal margin, and situated just at the outer margin of the costochondral junction. The sternum and the attached costal cartilages therefore seemed to bulge forward, increasing considerably the antero-posterior diameter of the chest.

All the superficial muscles appeared distinctly pale and quite thin. The pectoralis major, for example, measured only 3 mm. in thickness. The muscle substance, though pale, seemed to contain no obvious fat except as it lay in the septa between the muscle bundles. Thus one was at once impressed by a difference in appearance between this muscle and that found in cases of muscular atrophy. The muscles of the arms and legs were not different in character from those of the trunk. Here likewise the only abnormality seemed to be the striking lack of bulk and pronounced pallor. The intercostal muscles were thin and pale and in bulk proportional to the more superficial muscles.

Heart (No. 10845), weight, 50 grams; measurements:

Tricuspid valve	5 cm.
Pulmonary valve	3 cm.
Mitral valve	4 cm.
Aortic valve	3 cm.
Left ventricle wall (base)	8 mm.
Right ventricle wall (base)	3 mm.

Nothing grossly or microscopically abnormal was found in the heart.

Lungs: In both cases an extensive lobular pneumonia was found which in numerous areas showed itself microscopically to be of typical interstitial type. Much of the lung tissue which appeared collapsed on gross inspection showed widespread inflammation when examined more minutely. Associated with the pneumonia, which was shown to be of Pneumococcus Type IV origin by cultures from Case No. 10845, was marked inflammation of the bronchi. The visceral and parietal pleura was normal.

Abdominal Viscera: Nothing abnormal was found in any of the abdominal viscera. The weights and measurements of the organs from the two cases were so nearly the same that either might have been substituted for the other. The diaphragm seemed normal in comparison with that of normal cases of the same age.

Organs of Internal Secretion: The thyroid, parathyroids, adrenals, thymus, pituitary, pineal and ovaries were all carefully examined and no abnormalities found.

Brain, Spinal Cord and Peripheral Nerves: On gross examination of both cases the brain seemed somewhat atrophied, as indicated by widening of the sulci and shrinkage of the convolutions. Nothing was found to account for this. When the brain was sectioned grossly the usual normal structures were seen. There was no dilatation of the ventricles and no obstruction to the various passages of the ventricular system. In microscopic sections from all the important cerebral structures nothing abnormal was recognized.

The gross appearance of the spinal cord was in no way remarkable. When studied in microscopic sections with appropriate stains the various tracts were found normal. The nerve cells of the posterior horn of the gray matter seemed normal and as numerous as in normal cords of the same age with which comparisons were made. In view of the

often repeated statement that the cells of the anterior horn are diminished in number in cases of amyotonia congenita especial attention was directed to this portion of the gray substance. And indeed the impression was gotten from many sections that an actual paucity of large motor cells did exist at practically all levels of the cord. This impression was emphasized by comparison with preparations made from normal cords of the same age.

That some clear-cut abnormality did exist in the gray matter of the anterior horn was further emphasized by the character of the nerve roots leading out from this part of the cord. The nerve trunks composing the anterior roots were hardly more than one-third the size of the corresponding posterior roots and were practically destitute of myelin sheaths, a defect which produced a striking contrast between the anterior and posterior roots as they appeared in the same section stained by Spielmeyer's method (See Fig. 1 and Fig. 2). Since this difference between myelinization of the two roots appeared constantly and uniformly in sections from different levels of the cord, all stained individually and by the same technique, any error in technique which might have given this difference in appearance seemed to be satisfactorily eliminated. This interpretation was further supported by the lack of myelin sheaths found in many of the bundles of the peripheral nerves.

All the usual staining methods were used in an attempt to demonstrate some evidences of destructive processes and their consequences, but nothing could be found to indicate that any recent injury had occurred, either in the gray substance of the cord or in the nerves themselves.

Axis cylinders were found in such small numbers in the anterior roots that the impression relative to the paucity of motor cells seemed to be confirmed. The anterior roots, therefore, were composed of practically nothing but supporting tissue. This same structure was observed in many of the peripheral nerve bundles and such bundles were regarded as the motor fibres in contrast to the quite normal afferent trunks.

Voluntary Muscles: Muscles from the thigh, the abdominal wall, the chest wall, the diaphragm and the arm were studied in section. The diaphragm was somewhat different from the other muscles. Here the muscle seemed relatively normal, although occasionally fibres were

seen that were smaller than those of a normal child of corresponding age and which were not entirely unlike the abnormal ones seen in other muscles. Muscle from other locations, as noted above, presented the appearance described as characteristic of cases of amyotonia congenita. The usual distribution of fibres into bundles surrounded by epimysium, perimysium, etc. obtained. Although the bands of connective tissue separating the various bundles of muscle were found to be somewhat thicker than usual in the normal, this condition could hardly be interpreted as evidence of replacement of formerly injured muscle by scar tissue. Within the muscle bundle there was no fatty tissue and nowhere within the muscle fibres could fat droplets be demonstrated. Lying within the connective-tissue septa were numerous muscle spindles some of which appeared unusually large, although in every other respect quite normal. Nerve bundles were seen in normal number. Nothing remarkable was noted in connection with the blood supply to the various muscles and the individual muscle bundles.

The greatest variation was found in the appearance of the individual muscle fibres (See Figs. 4 and 5). The predominant fibre was small, the diameter not exceeding that of the cross section of its own muscle nucleus. A clear-cut sarcolemma sheath with sarcolemma nuclei could not be recognized, although in cross section the sarcoplasm maintained itself in a discrete, well rounded, mass in which the muscle nuclei lay. In longitudinal sections of such fibres both cross and longitudinal striations were seen, although the former were less distinct in some fibres. Muscle nuclei were not unusually numerous and they showed no evidence of abnormal proliferation. They were usually quite separated from each other, each maintaining its spherical or spindle shape, thus producing a picture quite unlike that of the muscle fibres in the various types of muscular atrophy. The appearance of these muscle fibres, was, on the contrary, identical with that of certain stages of development of embryonic muscle, such as may be seen in the embryo itself or in regenerating muscle as it occurs in the voluntary muscles following degeneration accompanying certain infectious diseases. This predominant type of fibre was present in bundles from which all other types were excluded or scattered diffusely among other fibres of the type described below.

Less frequently met with were fibres of normal size and structure.

These comprised only a fractional part of the muscle and rarely occurred in complete bundles to the exclusion of other types (Fig. 4).

Scattered among the embryonic fibres and the less numerous normal fibres a third type was found. These fibres were two or three times larger than the normal fibres of the muscle under consideration, and

FIG. 1. PHOTOGRAPH OF ANTERIOR OR MOTOR NERVE ROOTS AFTER STAINING FOR DEMONSTRATION OF MYELINE SHEATHS BY SPIELMEYER'S METHOD

Myeline sheaths are almost completely absent. Compare with the posterior root in the same section of the cord pictured in figure 2.

very often showed a peculiar glassy hyaline structure in which striations were difficult to make out except under the higher magnifications (Fig. 5). This incomplete hyalinization represented the only change observed in the muscles resembling in any way those which are common to the true myopathies. Since both the individuals under consideration died of an acute pulmonary infection, in which

hyalinization of voluntary muscle is known to be not uncommon, the hyalin changes just noted were regarded as probably resulting from the terminal infection and not a part of the amyotonia complex.

Discussion: The complete clinical and pathological record given above is that of two identical twin sisters. The clinical studies were

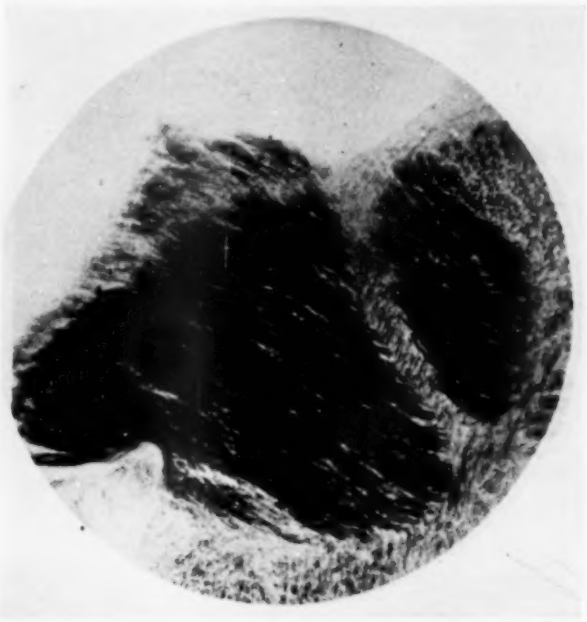

FIG. 2. PHOTOGRAPH OF POSTERIOR OR SENSORY NERVE ROOT AFTER STAINING FOR DEMONSTRATION OF MYELINE SHEATHS BY SPIELMEYER'S METHOD

The photograph is taken from the same section of the cord represented in figure 1. Myeline sheaths are normal in number.

such as to point definitely to the diagnosis of amyotonia congenita (Oppenheim's disease) and the pathological studies revealed all the lesions which have been identified with the disease in cases studied by other workers (1).

Since nothing whatever is known of the etiology of amyotonia congenita our interest in these two cases was stimulated by the possibility

of finding some clue to the causal factor in the fact that the two cases developed in twins arising from the same ovum. This fact and the absence of any familial history (in none of the reported cases was there any evidence of the disease being familial) suggests very strongly that the cause of the disease is to be found associated with the developing ovum. Two possibilities suggest themselves.

FIG. 3. LOW-POWER PHOTOGRAPH OF EMBRYONIC TYPE OF MUSCLE FIBRES REPRESENTING THE GREATER PART OF THE VOLUNTARY MUSCLES, AS SEEN IN LONGITUDINAL SECTION

The first of these is that in the course of maturation and subsequent fertilization of the ovum some element was left out or some derangement occurred which gave rise to imperfect subsequent development of the ovum. Had such a thing occurred, it must have been a most minute and indeed extraordinary alteration of the germ, since only those elements predestined to influence the development of the anterior

horn cells of the cord were involved. Assuming that such a defect did exist, it must have arisen very early in the life of the ovum, indeed within that period when the individual cells formed by the developing ovum still possess their totipotency and are capable of giving rise to complete individuals. Under no other circumstances except by

FIG. 4. MEDIUM-POWER PHOTOGRAPH OF CROSS SECTION OF MUSCLE FROM CASE NO. H-10845

The section shows the variation in size and character of muscle bundles and individual fibres.

accident or chance could the disease have occurred in both of the twins. This explanation is indeed a difficult one upon which to pin a strong faith but its possibility can hardly be denied.

As opposed to this hypothetical developmental defect is the second possibility of the lesions having been produced by some injurious agent relatively late in the life of the two embryos. One can readily conceive

of an injury to the spinal cord motor cells such as to cause the destruction of a large proportion of them or a retardation in their development as the natural result of some agent passed on to the embryo through the placenta from the infected mother. The thing suggested is of course some process similar to poliomyelitis. That no evidences for

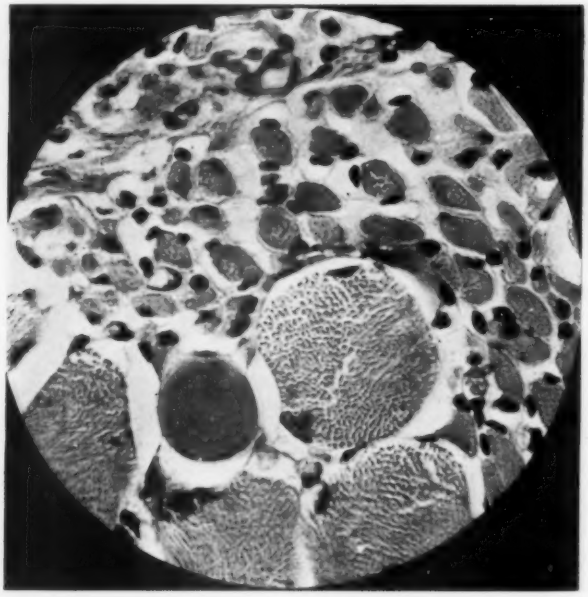

FIG. 5. HIGH-POWER PHOTOGRAPH OF A PART OF THE LOW-POWER FIELD SHOWN IN FIGURE 4

Three types of muscle fibres appear in the field, viz.: (*1*) A relatively normal size fibre which presents a hyaline more or less homogeneous sarcoplasm; (*2*) oversized fibres whose inner structure is unusually prominent; (*3*) fibres of the embryonic type which compose the bulk of the muscle.

such an inflammatory disease could be found in the course of the pathological studies is of little significance as against this theory, since such negative findings may be satisfactorily explained on the basis of the lesion having occurred at such an early date that all sign of it disappeared in the subsequent development of the tissues.

This theory of intra-uterine injury seems reasonable only, in the first place, insofar as the observation that the number of anterior horn cells in the cord is abnormally small is correct, and secondly, insofar as the continued development of voluntary muscle is dependent upon its nerve supply. As regards the first condition, there is some reasonable doubt in the absence of actual numerical count of the anterior horn cells in comparison with normal cords of the same age. Without carrying out this actual count, however, there seemed in these cases to be certainty as to the abnormally small number of motor cells, especially in view of the almost complete absence of axis cylinders as well as myeline sheaths in the anterior nerve roots. It is of course obvious that without anterior horn cells there could be no axis cylinders and vice versa.

The relation of nerve supply to the continuous growth of muscle is well understood. It has been shown from embryological studies that muscles can and do develop at least up to a certain point without nervous control (2). It has been shown also that muscle without nerve connection regenerates following complete or total degeneration of the sarcoplasm (3). It has been shown likewise that these regenerating muscle fibres have many, if not all, the characteristics of embryonic muscle (4) (5) (6). There is, on the other hand, no conclusive evidence to show that the regenerated muscle fibre ever reaches complete maturity without establishing a nervous connection. One may perhaps, therefore, feel justified in saying that without proper innervation any given muscle could not advance in its development beyond a point where its fibres could still be recognized as of late embryonic type. It is this stage of muscle development which appears to us to be characteristic in the cases of amyotonia congenita.

If it be assumed that an injury to the anterior horn cells of the cord occurred within that period of muscular development when nervous control first begins to manifest itself, then the theory of intra-uterine injury becomes indeed attractive, for it offers a satisfactory explanation of the mixture of normal and embryonic fibres in the same muscle bundle. The embryonic fibres would therefore seem to be those without nerve supply, the appropriate motor cells having been destroyed or prevented from developing by the injury, and the mature ones those with normal nerve connection. The estimated proportion of normal

muscle fibres to anterior horn cells and their correspondingly normal anterior root fibres in the cases under discussion is not out of harmony with this idea.

In the absence of any satisfactory understanding of the origin of these cases of amyotonia congenita as well as of those we have found in the literature, our inclination is naturally to place the greater emphasis upon that explanation of the lesions to which there appear the smallest number of objections; and that explanation seems to be the one based on some injury to the developing embryo which localizes especially in the anterior horn of the gray matter of the spinal cord, the condition of the muscles being secondary to this injury. When viewed in this way, amyotonia congenita comes to fall obviously outside of the group of true myopathies.

REFERENCES

(1) GRINKER: The Pathology of Amyotonia Congenita (A discussion of its relation to infantile progressive atrophy). *Arch. Neurol. and Psych.*, 1927, xviii, 982.

(2) KEIBEL AND MALL: Human Embryology, Vol. I, p. 482. Lippincott, Philadelphia, 1910.

(3) KIRBY: Experimentelle Untersuchungen über die Regeneration des quergestreiften Muskelgewebes. *Beitr. z. path. Anat. u. z. allg. Pathol.*, 1892, xi, 302.

(4) FORBUS: Pathologic Changes in Voluntary Muscle: I. Degeneration and Regeneration of the Rectus Abdominis in Pneumonia. *Arch. of Path. and Lab. Med.*, 1925, ii, 318–339.

(5) *Idem:* Pathologic Changes in Voluntary Muscle: II. Experimental study of Degeneration and Regeneration of Striated Muscle with Vital Stains. *Ibid.*, 1926, II, 486–499.

(6) VOLKMANN: Ueber die Regeneration des quergestreiften Muskelgewebes beim Menschen und Säugetier. *Beitr. zur path. Anat. u. z. Allg. Pathol.*, 1893, xii, 233.

PRACTICAL CONCLUSIONS DRAWN FROM ONE THOUSAND FORCEP DELIVERIES[1]

H. J. STANDER, M.D.

The two most important problems in obstetrics in this country are the appalling maternal mortality and the high death rate in the newborn. We, as obstetricians, cannot be proud of the former, nor can we claim to have materially reduced foetal mortality during the past generation, except by the prenatal treatment of syphilis and perhaps by the more frequent employment of Caesarean section in patients with contracted pelves. It is only by an honest acknowledgment and careful study of our bad results, rather than by directing attention to our occasional satisfactory successes, that we shall be able to raise the standard of obstetrical practice and thus reduce these death rates.

In this discussion we shall concern ourselves more with foetal death rate, although the maternal mortality will also be mentioned in considering our problem. An analysis of the foetal mortality in this Clinic in viable babies shows that asphyxia and birth injuries are responsible for 19 and 3 per cent of all deaths, respectively. As our tables show that about one-half of the foetal deaths following forceps were due to these two causes, it seemed to us that their study might help to show us in what way such a mortality may be reduced. Furthermore, our study seemed further justified in view of the recent trend toward an increased frequency of operative delivery by such means as prophylactic forceps and version and extraction. In our urgent desire to save the woman from the suffering and ill-effects of labor, it is well that we constantly bear in mind the interests of the offspring.

This paper is based upon the analysis of one thousand consecutive forceps deliveries performed in the Obstetrical Department of the Johns Hopkins Hospital from October 17, 1917, to December 31, 1929—a period of slightly over twelve years. It shows that in 15,370 full-term deliveries, the incidence of forceps delivery was about 9 per cent, or 1 in 11.

[1] Read before the Medical Society of the State of New York on June 3, 1930.

INDICATIONS

In Table I are shown the various indications for forceps delivery.

Uterine inertia, under which are included all cases in which the prolongation of the second stage was not due to one of the conditions mentioned below, constitutes the indication for forceps in over one-half of the total number. Inadequate pains throughout the entire course

TABLE I

Indications for forceps delivery

INDICATION		NUMBER OF CASES
Uterine inertia		543
Foetal distress		160
Abnormal course in posterior presentations		82
a. Deep transverse arrest	69	
b. Total failure of rotation	13	
Toxemias:		57
a. Eclampsia	36	
b. Pre-eclampsia	21	
Maternal exhaustion		37
Infection, intrapartum		31
Pelvis, funnel		21
Previous Caesarean section		16
Cervical dystocia		10
Rigid perineum		8
Prolapsed cord		8
Tetanic contraction of uterus		6
Maternal disease		8
a. Cardiac	5	
b. Tuberculosis	3	
Placenta praevia		5
Compound presentation		2
Premature separation of placenta		2
Face presentation		2
Congenital malformation of vaginal outlet		1
Teaching		1

of labor, as well as the secondary inertia following a test of labor in cases of moderate disproportion between the size of the head and pelvis, are the main factors in this group of cases. Patients with pelvic outlet contractions, with posterior presentations ending in failure of rotation, with cervical dystocia, with rigid perineum or with exhaustion in the second stage are not included in this group.

Foetal distress, as evidenced by the child's pulse or the presence of meconium, constitutes the second largest indication for forceps delivery.

It is interesting to note that an abnormal course in obliquely posterior presentations resulting either in complete failure of rotation or in deep transverse arrest called for the application of forceps in over 8 per cent of our cases, and in them deep tranverse arrest was five times more frequent than complete failure of rotation.

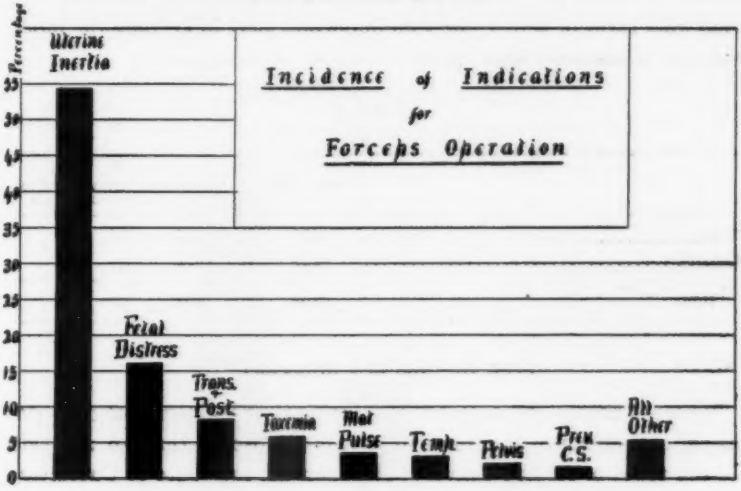

FIG. I

Eclampsia and pre-eclampsia account for over 5 per cent of the forceps deliveries. Our routine procedure in the treatment of eclampsia includes the application of forceps as soon as the cervix has become completely dilated, in an attempt to save the patient a long second stage, provided it can be done without the use of deep general anaesthesia.

Maternal exhaustion, as evidenced by the patient's pulse and general condition, constitutes only 3.7 per cent of the total indications, a surprisingly low figure, which is not greatly increased when intrapartum infection is added. The same may be said of funnel pelvis, as we find

that in only 2.1 per cent of our patients did a bony contraction of the pelvis require operative interference. The other indications make up a small percentage of the total, as will be seen from a study of Table I and Figure I.

PARITY

Our figures show that forceps delivery is four times more common in primiparae than in multiparae. This holds true for both races, as is shown in Table II. When discussing foetal mortality, we shall see that this ratio of 4 to 1 plays an important part in keeping the mortality at a relatively high figure.

TABLE II

Parity

	PRIMIPARAE	MULTIPARAE	RATIO PRIMIPARAE TO MULTIPARAE
White	481	116	4.1
Colored	327	76	4.3
Total	808	192	4.2

TYPE OF FORCEPS DELIVERY

There is hardly any better index for revealing the degree of conservatism or radicalism practised in a lying-in hospital than an analysis of the types of forceps delivery; although the incidence of Caesarean section, or version and extraction are perhaps equally good criteria.

We term the operation low forceps when the presenting part rests upon the perineum or is below the level of the ischial spines; when it is at or just above the level of the ischial spines the operation is mid forceps, and when the presenting part has partially descended into the pelvis but its greatest diameter is still above the superior strait, we speak of high forceps.

In our series of patients, low forceps was performed in 83.6 per cent of cases, mid forceps in 14.5, and high forceps in only 1.9 per cent. These incidences are graphically shown in Figure II, which strikingly reveals the predominance of low and the relative rarity of high forceps, and shows that our practice has been very conservative.

CONTRACTED PELVES

Contracted pelvis is a factor in the incidence of forceps operations. Our figures show that contraction of the pelvic outlet, or funnel pelvis, accounts for about 3 per cent of the forceps deliveries; whereas marked contraction of the pelvic inlet plays no part. On the other hand, such minor contractions as justify a so-called test of labor play an important part. In many such cases, the uterus exhausts itself in bringing about moulding of the foetal head, with the result that by the time it has descended into the pelvic cavity signs of uterine inertia, maternal

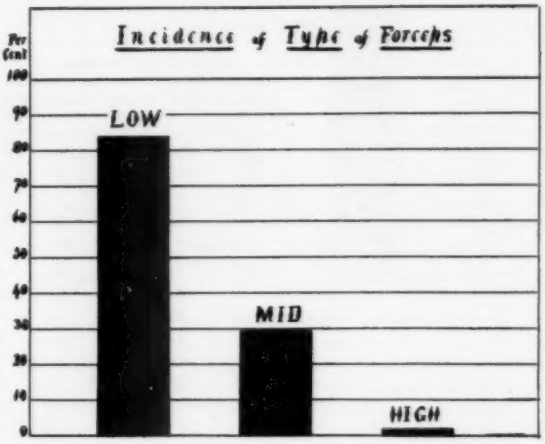

FIG. II

exhaustion or foetal distress appear, and necessitate the use of forceps. In such circumstances, the actual indication is inertia uteri, maternal exhaustion or what not; and the pelvic contraction is not the true indication. However that may be, such applications of forceps will occur more frequently in conservative than in radical clinics.

The general incidence of contracted pelves in our white and colored patients is 19.8 and 45.7 per cent, respectively; whereas in this series of forceps operations it increases to 27.8 and 56.1 per cent, respectively. Were pelvic contraction an important indication, one would expect

the incidence of forceps to be more than twice as great in the colored patients; but the reverse holds true, as it was only 7.1 per cent in the colored, as compared with 11.1 per cent in the white patients. This cannot be entirely explained by the smaller size of the colored child, as our figures show that its average weight is only 190 grams less than the white child. It is commonly stated that the head is more readily moulded in colored children, and this must undoubtedly be a factor in the production of the higher incidence of forceps in white women. It may also be stated that the average age of the white patients, both

TABLE III

Type of pelvis

TYPE	WHITE		COLORED		TOTAL	
	Primiparae	Multiparae	Primiparae	Multiparae	Primiparae	Multiparae
Normal	353	81	149	28	502	109
Funnel	76	13	62	7	138	20
G. C. T.	21	5	40	8	61	13
G. C. F.	8	3	21	3	29	6
G. C. R.	3	2	41	19	44	21
G. C. R. F.	1	0	5	0	6	0
Simple flat	3	8	3	1	6	9
Flat R.	1	2	2	3	3	5
Flat F.	1	1	0	1	1	2
Kyphotic	2	0	0	1	2	1
Other types	3	0	1	5	4	5
Unknown	9	1	3	0	12	1
Total Normal	72.2%		43.9%		61.1%	
Total Contracted	27.8%		56.1%		38.9%	

primiparae and multiparae, is several years above that of the black. From this one might reason that the heads of the white children would tend to be larger and harder, and that a rigid perineum as well as uterine inertia would more frequently necessitate the application of forceps in white women.

FOETAL MORTALITY

Our gross foetal mortality in forceps delivery is 10 per cent. We have studied this question from several different angles and have come to some rather surprising conclusions.

From Table IV it will be noted that the gross death rate is considerably higher in primiparae than in multiparae, being 10.5 in the former and 7.8 per cent in the latter, and even when the pelvis is normal the mortality is 7.6 and 5.5, respectively.

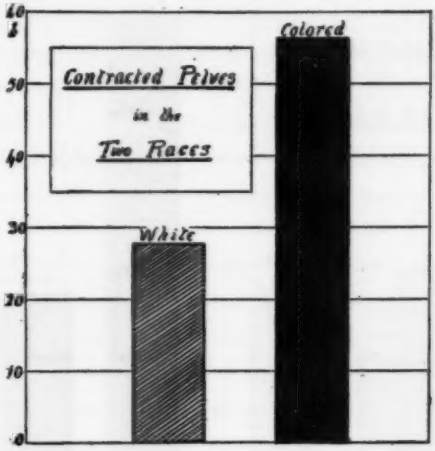

FIG. III

TABLE IV

Foetal mortality according to pelvis expressed in percentage

PELVIS	BOTH RACES		
	Primiparae	Multiparae	Total
Normal	7.6	5.5	7.2
Funnel	14.5	0	12.7
G. C.	14.4	26.3	16.5
Rhachitic	18.8	7.7	15.2
Other	16.0	11.1	13.9
Total	10.5	7.8	10.0

From the same table it will also be seen that in both races the death rate is about twice as high in contracted as in normal pelves. This holds true for each of the various types of contracted pelvis.

One of the most striking features in connection with the foetal mortality is the fact that in colored primiparae the rate was over twice as great as in white primiparae (17.4 and 5.8 per cent); whereas it was

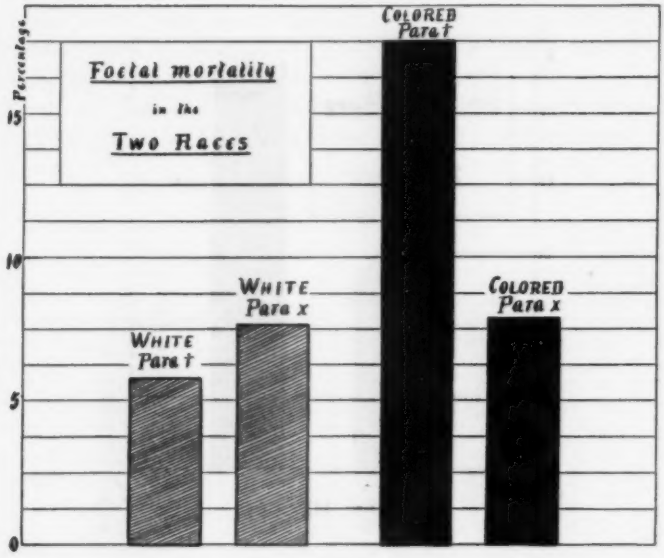

FIG. IV

TABLE V

Foetal mortality according to presentation

PRESENTATION	NUMBER OF CASES	FOETAL MORTALITY
		per cent
L. O. A. and R. O. A.	468	7.5
L. O. P. and R. O. P.	290	10.7
L. O. T. and R. O. T.	226	13.3
Others (Face, Compound, etc.)	16	25.0

essentially the same in black and white multiparae (7.9 and 7.8 per cent). Table VIII shows that it is because of this excessive mortality in black primiparae that the gross mortality for the series totals 10 per

cent, and also were it not for the colored patients in general that the mortality would scarcely exceed 6 per cent.

An analysis of the foetal mortality according to presentation also reveals instructive results. These are shown in Table V and Figure V. In anterior presentations the death rate is only 7.5 per cent, while in obliquely posterior presentations, it is 10.7, and increases to 13.3 and 23 per cent in deep transverse arrest and in face, brow and compound presentations, respectively. It is interesting to note that the mortality

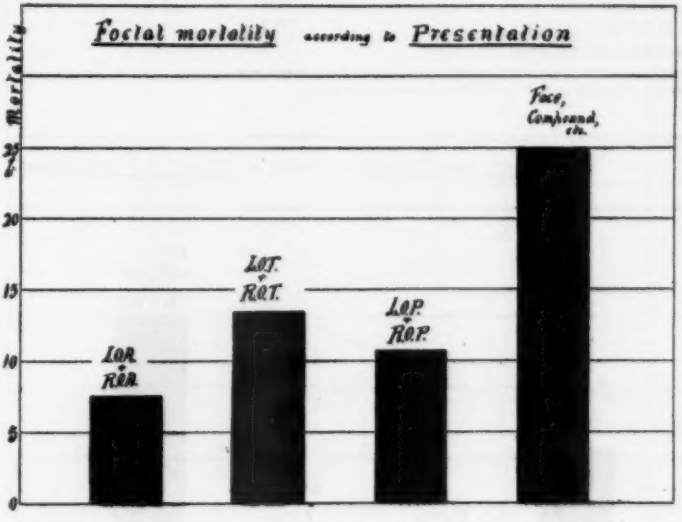

FIG. V

is higher in deep transverse arrest than in obliquely posterior positions. This is perhaps due to the fact that in the former the second stage is longer, and that mistakes in diagnosis lead to improper application of the forceps blades.

However that may be, we can state definitely that wherever anterior rotation from a posterior presentation fails to occur the foetal mortality attending forceps operation is twice that of primary anterior presentations. In this Clinic, all types of posterior presentations make up only about one-third of all presentations, yet in this series

they constitute somewhat over one-half. Such figures clearly indicate the more serious prognosis in posterior presentations, and emphasize their importance in increasing the necessity for the application of forceps.

TABLE VI

Foetal mortality according to time of admission in percentage

TIME OF ADMISSION	WHITE	COLORED	BOTH RACES
Before labor	10.0	25.0	15.7
Early in labor	4.4	11.3	7.3
Late in labor	5.7	16.3	9.9
After attempted delivery			25.0

Note: "Before labor" includes test of labor cases.

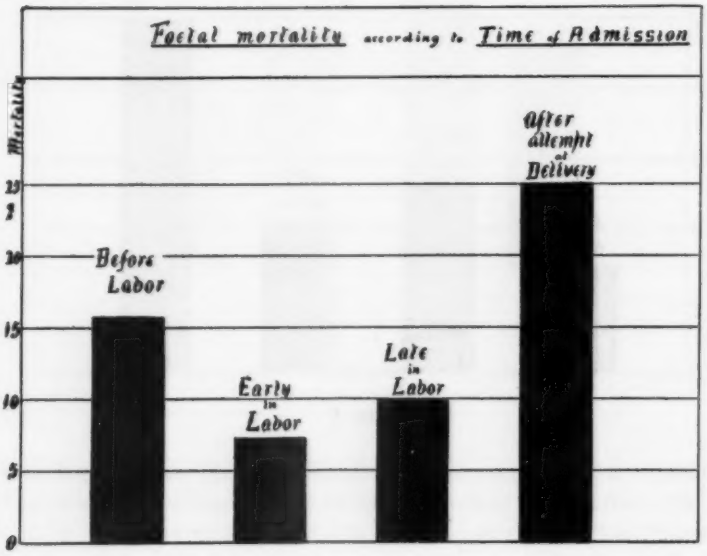

FIG. VI

A study of the foetal mortality according to the time of the patient's admission to the hospital shows, as one would expect, a higher death rate when she is admitted late in labor than when admitted early,

as well as an appalling mortality of 25 per cent when an attempt at delivery had been made prior to admission. The outstanding feature in this study of mortality according to time of admission, as shown in table and figure VI, is to be seen in the group admitted before labor, which naturally includes all patients with contracted pelves who were given a test of labor. The total child death rate in this group is 15.7, and is two and one-half times higher in blacks than whites. Further-

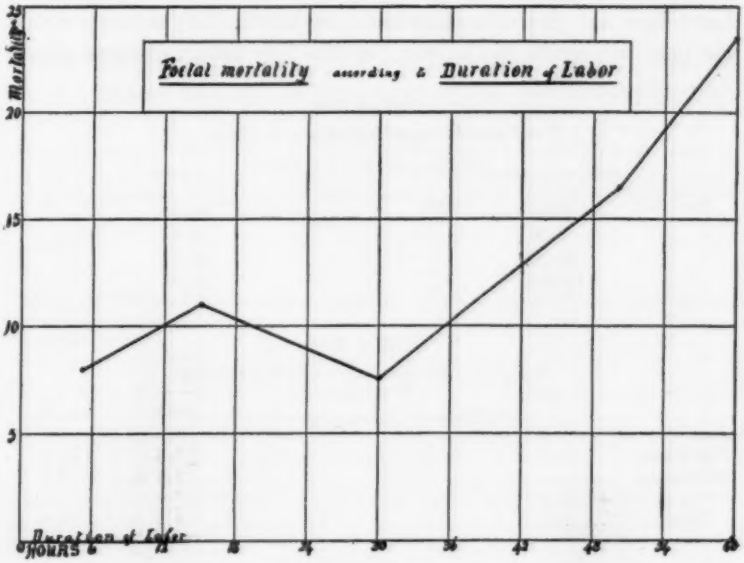

FIG. VII

more, in each race it is higher than when the patients were admitted early or late in labor. This does not speak so well for forceps operation on patients with slight disproportion, who have been given a test of labor.

An analysis of the effect of the duration of labor on foetal mortality reveals rather unsuspected results. One might have expected to find a slightly higher death rate accompanying long labors, but certainly not such a sharp rise beyond the 36 hour mark, as is shown in Table VII and Figure VII. In patients in labor not longer than 30 hours the

death rate is only 8.8 per cent, but when the labor lasts from 36 to 48 hours the rate is almost doubled, while when the duration exceeds 50 hours the foetal mortality approaches 25 per cent. These figures indicate that we should pay more attention to the duration of labor in the interests of the offspring, and particularly when it exceeds 36 hours. Undoubtedly we often do not appreciate to what risks the child is subjected during a 48 hour labor, no matter whether delivery be effected by forceps or not. It seems that the behavior of the foetal heart does not give us an absolute index of this risk; and only within the past two weeks the author has seen two babies succumb after a

TABLE VII

Foetal mortality according to duration of labor

DURATION OF LABOR	BOTH RACES
hours	*per cent*
0–30	8.8
30–50	16.3
Over 50	23.3

TABLE VIII

Foetal mortality according to race in percentage

PARITY	WHITE	COLORED
Primiparae	5.8	17.4
Multiparae	7.8	7.9
Total	6.2	15.6

labor of 60 hours, which was terminated by a very easy low forceps, and with the foetal heart regular and of normal rate at the beginning of the operation. In each case, autopsy showed cerebral damage, which did not manifest itself by changes in the foetal heart rate.

INCIDENCE OF LACERATIONS

In Table IX we note that cervical lacerations occurred in 8.8 per cent of the patients. This seems to be an argument in favor of not routinely examining the cervix after forceps delivery except in the presence of bleeding, although it is probable that more of our patients

had cervical tears which escaped diagnosis because of the absence of bleeding.

First degree perineal lacerations occurred in one-third of our patients, second degree tears, including episiotomies, in 40 per cent; and third degree in 2 per cent. It is noteworthy that only one-fifth of the patients had no perineal tears, which may be regarded as an argument in favor of routine episiotomy in the primiparous woman.

MATERNAL MORBIDITY

Only 64.6 per cent of all patients were afebrile, and we note that the rise in temperature was attributed to puerperal infection in about 30

TABLE IX

Incidence of tears in percentage

TYPE OF TEAR	WHITE	COLORED	BOTH RACES
Cervical	8.5	9.2	8.8
Perineal 1st degree	34.2	32.5	33.5
Perineal 2nd degree	42.0	37.7	40.3
Perineal 3rd degree	1.5	2.5	1.9
No perineal tears	22.3	27.3	24.3

TABLE X

Puerperal morbidity percentage

	WHITE	COLORED	BOTH RACES
Afebrile	72.2	53.3	64.6
Puerperal infection	21.3	42.9	29.7
Febrile (other causes)	6.5	3.8	5.7

per cent. Here, as in other studies on morbidity from this Clinic, the colored patient is more prone to infection than the white, as is shown by the fact that the incidence of puerperal infection was 42.9 and 21.3 per cent in the two races, respectively. Accordingly, it would seem that the colored patient, due perhaps to a fundamental biological inferiority, is about twice as poor a risk as the white patient.

MATERNAL MORTALITY

Of the thousand women, eleven died, a gross mortality rate of 1.1 per cent. Of the deaths, 7 occurred in the 403 colored patients, giving

a mortality rate of 1.7 per cent for the black as compared with 4 in 597 white women, or 0.7 per cent. This ratio is very similar to that noted in the morbidity in the two races, as was mentioned above.

A further analysis of the maternal mortality shows that the causes of death were as follows:

Eclampsia	4
Anaesthesia	2
Postpartum hemorrhage	1
Puerperal infection	1
Pneumonia	1
Pulmonary embolus	1
Pulmonary oedema	1

Careful consideration of this list indicates that the majority of the deaths were not due to the forceps delivery *per se*, but in great part to the underlying complication, which made it necessary.

CONCLUSIONS

1. Low forceps constitutes over 80 per cent of all forceps delivery, while high forceps was performed in less than 2 per cent of the cases.
2. Uterine inertia or prolonged second stage of labor accounts for over half the forceps operations.
3. Forceps delivery is necessary four times more frequently in primiparous than in the multiparous patients.
4. Contracted pelvis occurs more than twice as frequently in the colored as in the white patient. It is a considerable factor in the indication for forceps, since it not only includes contraction of the pelvic outlet due to funnel pelvis, but also plays a considerable part in the production of uterine inertia, in patients who are subjected to a test of labor.
5. The gross foetal mortality incident to forceps delivery is 10 per cent.
6. The foetal mortality in colored primiparae is 17.4 per cent, and constitutes the most important single factor in the production of the high gross mortality in forceps delivery.
7. The foetal death rate is definitely increased by failure of rotation in posterior presentations, and is particularly high where the head is arrested in deep transverse.

8. The duration of labor is a very important factor in increasing the foetal mortality incident to forceps delivery. After 48 hours the foetal death rate becomes excessively high.

9. Only one-fifth of patients delivered by forceps had no perineal lacerations. As tears are far more frequent in primiparae, primiparity may be an argument in favor of routine episiotomy.

10. Our experience shows that the colored woman is about twice as poor a risk as to both morbidity and mortality, as the white patient.

11. The cephalic application of the blades is essential to the proper performance of forceps delivery. The high incidence of obliquely posterior and of deep transverse presentations makes it inadvisable to apply the blades to the sides of the pelvis; and it is to neglect of this precaution that the great dread of such presentations is due.

12. The foetal heart *in utero* does not always afford satisfactory information as to the condition of the child, and this should be borne in mind especially when forceps are applied in women who have been in labor for more than 36 hours.

13. The foetal mortality is higher in primiparae than multiparae; and this is particularly true for forceps delivery in the young primipara under 20, as well as in the elderly primipara over 35 years of age.

14. From the considerations here adduced, it is apparent that the conservative use of the forceps is a means of saving the lives of many infants, but nevertheless, the foetal mortality is higher than is usually appreciated.

THE PATHOGENESIS OF THE FORMS OF JAUNDICE

ARNOLD RICE RICH

From The Department of Pathology, The Johns Hopkins Medical School

In recent years important advances have been made in the understanding of the formation and excretion of bile pigment. The various investigations which have placed our knowledge of these matters upon a surer footing have, very largely, been stimulated by the perplexities which have always been encountered in the attempt to form a clear idea of the underlying causes of the various forms of jaundice. The early pathologists soon learned from their gross dissections that while there were some cases of jaundice in which a mechanical obstruction to the outflow of bile through the ducts could be clearly demonstrated, there were many other cases in which no obstruction whatever could be found. This led to the familiar separation of all cases of jaundice into two groups, to one of which was given the descriptive term "obstructive jaundice," while the other was designated by the less informing expression "non-obstructive jaundice." Although certain finer details of the problem are still under investigation, there has never been any great difficulty in understanding the general nature of the mechanism of the jaundice which results from gross obstruction to the outflow of bile from the liver; but the mechanism of many of the forms of "non-obstructive" jaundice has been exceedingly difficult to fathom, and the attempts which have been made to classify these forms from the standpoint of pathogenesis have never been satisfying. The many, and often fantastic, theories advanced to explain the different varieties of jaundice without obstruction have long stood as clear enough evidence of the need of more precise information regarding the formation and excretion of the bile. Although the recent improvement in our understanding of the formation of bilirubin has finally satisfied the long-felt desire of students of jaundice for proof that bile pigment is

made outside of the epithelial liver cells, still, the possession of this proof does not at all permit us to regard the non-obstructive jaundices as simply "haematogenous" in origin. It is obvious that, regardless of where or in what quantity bile pigment is made, the liver must excrete it if jaundice is to be prevented; and that, therefore, in order to understand the non-obstructive jaundices one has always to take into account the excretory power of the liver under normal conditions, and under the conditions existing in the body of the individual in whom jaundice makes its appearance. Various aspects of the rôle played by the liver in jaundice have been under investigation in this laboratory for several years, and the results of these studies have led to the appreciation of certain principles which are of importance in the understanding of jaundice. The purpose of this paper is to set forth these principles, and to attempt to classify the forms of jaundice in the light of our present information regarding the pathogenesis of biliary retention.

In any discussion of jaundice we must set out from the established fact that bile pigment (bilirubin) is made outside of the epithelial liver cells, is carried to them by the blood stream and is excreted by them into the bile canaliculi (1) (2) (3). It is not known exactly which cells manufacture the pigment, but we do know that it is made especially within the bone-marrow, spleen and liver (4) (5), that there is no evidence that it can be made by extracellular ferments (10), and that there are very good reasons for believing that the phagocytic (reticulo-endothelial) cells common to these organs are responsible for its production (6) (7). The only known source of bile pigment is the haemoglobin from destroyed red blood cells.[1] It has been demonstrated that muscle haemoglobin can be converted into bilirubin (8), but there is no evidence that the former pigment acts as a source for the latter under normal conditions, or under pathological conditions associated with jaundice. The question of the origin of bilirubin

[1] The haemoglobin of the extravasated erythrocytes in haemorrhages is converted locally, apparently by the mononuclear (reticulo-endothelial) phagocytes, into a pigment which has been called 'haematoidin' but which Dr. Bumstead and I have shown to possess all of the characteristic physical and chemical properties of bilirubin. There is no reason whatever for regarding this pigment as an isomer of bilirubin, or as anything other than bilirubin itself (47).

has been dealt with at length in another place (9) and I shall not enter here into any further discussion of this matter other than to say that, in the light of our present information, the essential points in the physiology of bile pigment can best be outlined in the following manner: haemoglobin taken up from the blood stream by the phagocytic cells which are anchored within the capillaries of the liver (K, Fig. 2), spleen and bone-marrow is split, within those cells, into bilirubin and a colorless, iron-containing residue. Both of these substances are then discharged into the blood stream. In spite of its undoubted importance in the normal and pathological metabolism of haemoglobin, almost nothing is known of the nature or fate of the colorless, iron-containing residue of the haemoglobin molecule. The bilirubin, however, as it passes through the capillaries of the liver, is selectively taken out of the blood by the epithelial hepatic cells and is excreted, somewhat as a threshold substance, into the bile canaliculi, whence it flows, mixed with the rest of the bile, through the larger ducts into the duodenum. Although bilirubin itself can be absorbed back into the blood from the intestine and excreted again into the bile (11), most of the pigment reaching the intestines is reduced there to urobilin by the action of bacteria. Some of the urobilin so formed is excreted in the faeces, but some is absorbed into the blood. Under normal conditions most of the urobilin absorbed into the blood stream is removed by the liver to be excreted in the bile (11), or to be conserved for unknown purposes; but under certain conditions to be discussed below, the liver becomes unable to remove it efficiently from the blood stream and quite large amounts may pass from the blood into the urine.

It is clear, then, that there are several theoretically possible circumstances which have to be considered as possible causes of jaundice occurring in the absence of obstruction. Since, in order to prevent jaundice, the liver cells have to excrete efficiently the bilirubin brought to them by the blood stream, jaundice would occur (1) if the threshold of the liver for bilirubin excretion became greatly raised; (2) if, for any reason, bilirubin were produced faster than the normal liver cells could excrete it; (3) if the excretory mechanism of the liver were so disturbed that the amount of bilirubin normally produced could not be satisfactorily removed from the blood; and finally (4) if there occurred any combination of the above conditions.

The first condition mentioned is a purely hypothetical one, for the existence of which there is no evidence, and which, I believe, it is unnecessary to invoke in order to explain any form of jaundice.

The second possible condition—an uncomplicated excessive production of bilirubin—is rarely a cause of jaundice, for two reasons: first, because the normal liver is able to excrete much more bilirubin than is ordinarily delivered to it, and second, because an excessive production of bilirubin is, as we shall see, practically always associated with other conditions which tend to impair the excretory power of the liver. In regard to the first of these reasons, it is important to realize that in spite of the fact that, in the human being and in certain other animals, a small amount of bilirubin is retained normally in the blood stream after the manner of threshold substances, the normal liver has a very great reserve excretory power. The analogous reserve power of the kidney is perfectly familiar. It is well known that one kidney, or even less can suffice to maintain life. In a comparable manner there is normally a considerable excess of liver tissue above the amount necessary for the excretion of the bilirubin formed under normal conditions. Thus, although removal of the entire liver from the dog invariably results in jaundice (1) (2) (3), the excretory function of more than 95 per cent of the liver substance of the dog or the monkey can be abolished, and yet the remaining 5 per cent of liver tissue will suffice to prevent the development of jaundice (12). In the human being, the reserve power of the liver cells becomes clearly evident in various pathological conditions in which, in spite of a great reduction in the amount of functioning liver tissue, jaundice does not appear. I have, for example, seen the left hepatic duct completely occluded by a gall-stone without the occurrence of jaundice. The portion of the liver dependent upon this duct for drainage was slightly atrophied, but there was no appreciable hypertrophy of the remainder of the liver, the excretory power of which sufficed to prevent the appearance of jaundice. Such a case merely confirms, in the human being, the experimental observations made by McMaster and Rous upon animals (12). It is, furthermore, a familiar fact that jaundice is quite commonly absent in nodular cirrhosis even when there is marked loss of liver tissue which the compensatory hyperplasia falls far short of replacing. Again, it is well known that the greater part of

the liver may be destroyed and replaced by tumor metastases without any resulting jaundice if the larger bile-ducts are not obstructed by the tumor. The fact that the liver possesses a much greater capacity for excreting bilirubin than it is called upon to use normally makes it clear that up to a certain limit an over-production of bilirubin will be taken care of without the development of cutaneous jaundice. Just what this limit is in the human being is not accurately known, but the numerous pathological conditions in which the amount of pigment in the stools is greatly increased above normal in the absence of jaundice stand as evidence that marked increases in the amount of bilirubin produced can be excreted by the normal liver well enough to prevent visible jaundice. Of course, it is imaginable that if bilirubin continues to be produced in excess over a long period of time, as it is in various diseases, the excretory power of the liver might become impaired because of the continued strain put upon it. There is, however, no evidence that the liver actually does ever suffer an impairment of function from overactivity, and indeed, we should expect that an uncomplicated demand for increased work would, through the process of work-hypertrophy, increase the liver's efficiency, as in the case of other excretory organs, rather than depress it. However, even if an impairment of function does ever follow overstrain from excessive bilirubin excretion, it is clear that the jaundice in such a case could not be regarded as the result of an uncomplicated over-production of bilirubin; it would be a result of the combination of an increased demand upon the liver and a decreased excretory power of the liver; and this brings us to the second reason which I have given for the statement that jaundice rarely, if ever, results from simple over-production of bilirubin—namely, that over-production of the pigment is ordinarily associated with conditions other than mere overstrain which tend to depress the excretory power of the liver (*e.g.*, anoxaemia, febrile disease, immaturity of liver cells). I shall not dwell upon this latter fact here, for it will become evident below; these, however, are the reasons why the second theoretical possibility mentioned above—an uncomplicated over-production of bilirubin—is rarely the cause of jaundice.

As for the third possibility—the disturbance of the excretory mechanism of the liver to such a degree that the amount of bilirubin

produced normally cannot be excreted—this condition is undoubtedly responsible for certain cases of jaundice. It is important, however, to point out that there is no form of jaundice which is known to result purely from a *functional* depression of the excretory power of the liver, *i.e.*, without actual loss of cells through necrosis. We shall see in a moment that as long as all of the hepatic cells are alive, the considerable reserve excretory power which we have discussed above appears to be sufficient to compensate for any depression of function which occurs under various pathological conditions. In other words, there is no pathological condition which is known to impair the function of the living hepatic cells to such a degree that they are unable to prevent jaundice by excreting the amount of bilirubin normally formed. If, however, the total amount of functioning liver substance is reduced by necrosis and cellular damage, jaundice will result whenever the loss of liver tissue reaches a point at which the activity of the cells remaining alive is insufficient for the proper removal of the pigment from the blood (*e.g.*, acute yellow atrophy, yellow fever, chloroform poisoning).

I have pointed out that, largely because of the reserve power of the liver, it rarely happens that jaundice results from the mere production of a greater amount of bilirubin than the normal liver can excrete; and, on the other hand, that there is no condition known at present which can depress the excretory function of the living liver cells to such a degree that jaundice results because the normal daily amount of bilirubin cannot be excreted. Any impairment of the excretory function of the liver must, however, also decrease its reserve power; and it is therefore clear that while a liver with a reduced capacity for excreting bilirubin may be able to rid the blood of the amount of the pigment formed normally, if bilirubin is produced in excess such a liver may be quite unable to excrete it all, and jaundice will result from the retention of the excess pigment. This situation, which represents the fourth possibility mentioned above, is a quite common one for, as I have said, the conditions which are responsible for an increased production of bile pigment are almost always associated with conditions which depress the excretory function of the liver. There are, therefore, many cases of jaundice which result from the fact that a liver with an excretory function and reserve power lower than normal is called upon to excrete an excess of bilirubin.

From the above brief considerations it is obvious that whether or not jaundice will occur in any case depends upon the balance between the amount of bilirubin delivered to the liver for excretion and the capacity of the liver to excrete the pigment; and we shall see that with very rare exceptions the development of jaundice, even in the absence of obstruction, depends at least partly upon a lowering of the excretory ability of the liver.

The application of certain laboratory tests. In a thorough clinical analysis of any form of jaundice it is important to determine the physical state of the bilirubin present in the blood, the chemical form of the pigment present in the urine, and also to estimate, at least roughly, the relative quantity of pigment in the stools, blood and urine.

One of the most helpful contributions to the study of jaundice has been the application of Ehrlich's diazo-reaction as a test for bilirubin in albuminous fluids. This procedure, introduced and applied with well-known and important results by Hijmans van den Bergh (13), has been of the very greatest assistance, for not only can bilirubin be measured quantitatively when present in the plasma in even minute amounts, but the test fortunately happens to permit one to decide in most cases whether one is dealing merely with bilirubin which the liver has failed to remove from the blood, or with bilirubin which has passed through the liver cells into the bile canaliculi, but which has subsequently found its way back into the blood stream because of obstruction of the ducts, or because of necrosis of the liver cells. The value of being able to determine this much about the pigment which is accumulating in the blood and in the tissues in a given case of jaundice is too obvious to require comment. I shall not enter into a description of this now well-known test other than to mention that when it is applied to bilirubin which has not yet passed through the liver cells there occurs a delayed or so-called 'indirect' reaction; whereas, in contrast, bilirubin taken from the bile-ducts or from the gall-bladder, or that regurgitated into the blood from the bile canaliculi, gives a prompt, or 'direct,' reaction. There has been a great deal of speculation and investigation concerning the reason for this difference in reaction. It has been believed by some investigators that the bilirubin taken out of the blood by the liver cells is changed

in some way within those cells before being excreted into the bile. To others it has seemed more probable that the pigment is not really changed by the liver cells, but that there is some substance present in the bile which is responsible for the difference in the reaction—*i.e.*, that the type of reaction depends upon the medium in which the pigment is contained rather than upon an alteration of the pigment itself. This latter view has recently received strong support from the recent experiments of Barron (14) who has shown that, while pure bilirubin at the pH of the blood gives the direct or prompt reaction, if it be added to normal plasma it then gives the indirect reaction. This Barron believes to be the result of the adsorption of bilirubin by the plasma proteins, the pigment being in that way prevented from reacting promptly with the reagent. If, however, substances which have the property of lowering surface tension are first added to the plasma and then bilirubin is introduced, or if such substances are added to the plasma at the same time as the bilirubin, the reaction of the pigment remains direct, and this apparently for the reason that substances which lower surface tension seem to be adsorbed by proteins more readily than is bilirubin, and therefore the pigment remains free when present in solutions in which the protein molecules are covered with those substances. Barron has found that both bile salts and cholesterin are exceptionally potent in preventing the adsorption of bilirubin by the plasma proteins, and it is significant that these substances are present in whole bile and occur in increased amounts in the plasma in the various forms of jaundice in which the blood bilirubin gives the direct reaction.

Whatever may be the ultimate explanation of the different forms of the reaction, a great amount of experimental and clinical investigation has made it perfectly clear that when the plasma bilirubin in a case of jaundice is subjected to the van den Bergh test, the direct reaction indicates that whole bile, containing bile acids and cholesterin as well as bilirubin, has been regurgitated into the blood stream, and therefore that one is dealing either with obstruction of the ducts or with necrosis of the liver cells, for these are the two conditions which permit bile to escape from the canaliculi into the blood; the indirect reaction, on the other hand, informs us that the bilirubin in the plasma under examination has not been regurgitated into the

blood from the canaliculi, but that it represents pigment which the liver has not yet been able to remove from the blood stream. So much for the direct and indirect reactions. Sometimes, however, the reaction is intermediate between the direct and the indirect forms—a so-called 'diphasic' reaction. This form of reaction appears to result from the presence of a small amount of direct reacting bilirubin in plasma containing a large amount of indirect reacting pigment. According to Barron's view, a diphasic reaction would occur, for example, if bilirubin continued to be added to plasma, the proteins of which had already adsorbed all of the pigment they were capable of holding. This form of the reaction does not yield the clear-cut information which the pure direct or indirect reaction yields, for it can occur as a result of a high degree of pigment retention in the absence of regurgitation, or it may occur in certain stages of biliary regurgitation caused by obstruction or by necrosis of liver cells. Considered in relation to the findings in the stools and urine in a given case, however, it is frequently possible to determine whether the diphasic reaction results from the retention or from the regurgitation of bilirubin.

Another important aid in determining the pathogenesis of any particular case of jaundice is the fact that in those cases in which whole bile is regurgitated into the blood because of obstruction or of necrosis of liver cells, and in which, therefore, the bilirubin in the blood gives the direct van den Bergh reaction, the urine ordinarily contains bilirubin and may contain bile salts as well; while, in contrast, in the cases in which the cause of the jaundice is neither obstruction of the ducts nor necrosis of the hepatic cells (and in which, therefore, the blood bilirubin gives the indirect reaction) the urine contains neither bile salts nor bilirubin, but there is present an excess of the reduced form of bilirubin, urobilin. The character of the pigment present in the urine in jaundice is therefore of considerable significance. It is not yet entirely clear just why only the direct reacting bilirubin can escape readily from the blood into the urine; but if it be true, as it indeed seems to be, that the indirect reacting bilirubin is bound to plasma protein while the direct reacting bilirubin is not, it is clear that the latter form could be excreted more readily by the kidneys than the former.

The origin of at least a part of the urobilin which is present in the urine in increased amount in the cases of jaundice in which the blood contains the (presumably) protein-bound, indirect bilirubin, is clear enough. Certainly, some of this urine urobilin can be accounted for by the fact that in these cases, as we shall see, the amount of bilirubin excreted into the intestine is greater than normal and, being reduced in the intestine to urobilin, a greater amount of this latter pigment is available for absorption into the blood stream than is the case under normal conditions. Added to this increased production of intestinal urobilin is the subnormal function of the liver, which is normally concerned with removing from the blood the urobilin absorbed from the intestine. These two circumstances lead to the result that urobilin is not adequately removed from the blood by the liver, and the excess is excreted by the kidneys. It remains a question whether any of the bilirubin which stains the tissues in jaundice is reduced there to urobilin, thus providing another source of the urobilin which appears in the urine.

Finally, it is obvious that the relative amount of pigment excreted in the stools is also of importance in an analysis of any case of jaundice, for the amount of faecal urobilin is diminished whenever, because of obstruction or necrosis, the liver is unable to excrete bilirubin properly; and on the other hand, the amount of faecal urobilin is increased in cases of jaundice associated with an increased production of bile pigment in the absence of obstruction or widespread necrosis.

It is necessary to stress the importance of the most painstaking technique and observation especially in the use of the van den Bergh reaction and in the search for bilirubin in the urine by chemical means. A careless application of these tests will lead only to confusion.

CLASSIFICATION ON THE BASIS OF PATHOGENESIS

The classification of jaundice which is set forth in this paper is the result of studies which have been carried out during the past several years in the effort to understand clearly the pathogenesis of each of the various types of jaundice. The clinical and pathological conditions associated with each separate type have been carefully analyzed in the light of the available information relating to the formation and

excretion of bile pigment. In numerous instances in which the available data were insufficient to permit a satisfactory approach to a proper understanding, further experimental and clinical investigations were carried out in order to obtain the necessary information. Tables I and II present in a simple, schematic way the essential factors which these studies have indicated as being responsible for the appearance of jaundice in each of the numerous diseases which favor its development. In order to make clear the reasons for the different subdivisions in this classification, I shall discuss briefly, and in order, the facts upon which they are based. From this discussion it will be

TABLE I

I. Retention Jaundice *Laboratory tests:* Blood: ++ indirect v. d. Bergh Stools: ++ urobilin Urine: ++ urobilin *Cause:* Overproduction of bilirubin + subnormal liver function caused by	A. Anoxaemia, caused by	1. Anaemia	Pernicious anaemia Haemolytic jaundice Sickle-cell anaemia Paroxysmal haemoglobinuria Mismatched transfusion Phenylhydrazine poisoning
		2. Chronic passive congestion	Cardiac decompensation (especially with pulmonary infarction)
	B. Febrile disease, associated with anoxaemia resulting from	1. Anaemia	Haemolytic septicaemias Malaria Black-water fever
		2. Pulmonary consolidation	Lobar pneumonia
	C. Immaturity of liver cells in	Newborn	Icterus neonatorum
	D. Undetermined		Hanot's cirrhosis

evident that there are certain unsolved problems relating to some of the forms of jaundice. As long as these problems remain unsolved no classification of these forms, made on the basis of pathogenesis, can be regarded as final. However, as it stands, the classification offered in this paper is in keeping with our present information as set forth in the discussions of the various subdivisions, and it has been of the greatest practical service in the interpretation of the pathogenesis of the manifold types of jaundice which have come before us in the wards and in the autopsy room.

To begin with, any consideration of the matter should make it

TABLE II

II. Regurgitation Jaundice

Laboratory tests:
Blood: ++ direct v. d. Bergh.
Stools: decreased urobilin
Urine: + bilirubin and bile salts

Cause: Rupture of canaliculi, caused by

- **A. Necrosis of liver cells, caused by**
  - **1. Toxic agents**
    - **a. Chemical** — Chloroform; Carbon tetrachloride; Phosphorus; Salvarsan; etc.
    - **b. Vegetable** — Mushroom poisoning
    - **c. Bacterial** — Yellow fever; Congenital syphilis; Weil's disease
    - **d. Undetermined** — 'Idiopathic' acute yellow atrophy; Laennec's cirrhosis
  - **2. Severe degrees of A and B, Table I**
- **B. Obstruction of bile-ducts, caused by**
  - **1. Plugging**
    - **a. Calculi** — Cholelithiasis; Pancreatic calculi
    - **b. Inflammatory exudate** — Cholangeitis
    - **c. Parasites** — Fasciola hepatica; Ascaris; etc.
    - **d. Neoplasms** — Tumors of bile ducts
  - **2. Stricture**
    - **a. Scarring** — Chronic cholangeitis; Syphilitic cirrhosis
    - **b. Malformations** — Congenital stenosis or atresia of ducts
    - **c. Neoplasms** — Primary or secondary tumors involving bile-ducts
  - **3. Pressure**
    - **a. Inflammatory masses in liver** — Abscess; Gumma; Tubercle; Hodgkin's disease
    - **b. Parasitic masses** — Echinococcus cyst
    - **c. Vascular tumors** — Aneurysm of hepatic artery
    - **d. Inflammatory tissue outside liver** — Peritoneal adhesions
    - **e. Neoplasms** — Tumors of pancreas, gallbladder, liver, etc.
    - **f. Enlarged hepatic lymph nodes** — Tumor metastases; Hodgkin's disease; Tuberculosis
- **C. Undetermined** ..... Catarrhal jaundice

clear that the familiar separation of all forms of jaundice into the two classes, "obstructive" and "non-obstructive," is highly unsatisfactory. Obviously, any given case must be either obstructive or non-obstructive, but it is just as obvious that, since some cases of jaundice are caused by necrosis of the liver cells while others are not, one could quite as properly separate all cases of jaundice into those caused by necrosis and those not caused by necrosis—a division which would be entirely as logical and reasonable (and as entirely unsatisfactory) as that of "obstructive" and "non-obstructive." It should be remembered that this latter classification was never intended to be more than a crude make-shift, fashioned at a time when information about the physiology of the bile was very limited. Although it served the good purpose which every first step in the ordering of knowledge serves, this terminology also undoubtedly had the effect of retarding progress in the understanding of jaundice, for the term "non-obstructive" soon came to be used as comfortably as though it really conveyed positive information, whereas in fact it has, of course, no more meaning than the designation of an unconscious patient as a case of "non-nephritic coma" would have. But aside from the fact that it conveys no positive information regarding pathogenesis, the term "non-obstructive" includes cases of jaundice which differ so widely in their clinical and pathological manifestations that the forcing of them all into one group has served to confuse rather than to clarify the matter. To appreciate this one need only consider, for example, the clinical, to say nothing of the marked pathological differences between the jaundice associated with acute yellow atrophy and that associated with congenital haemolytic jaundice—both instances of so-called non-obstructive jaundice. In the former the blood bilirubin gives the direct van den Bergh reaction, the amount of faecal urobilin is diminished, and the urine contains bile salts and an abundance of bilirubin; in the latter the blood bilirubin gives the indirect reaction, the faecal urobilin is increased in amount, and the urine contains no bile salts and no bilirubin, but an abundance of urobilin. Obviously it is folly to group these two types of jaundice together simply because in both the bile ducts are patent.

I shall not dwell at length upon other proposed classifications of

jaundice, for none of them are really satisfying for practical use. Van den Bergh's (13) division into the two types, 'mechanical' and 'dynamic' jaundice, is virtually only a renaming of the obstructive and non-obstructive classification. McNee's proposed classification (15) enjoys, perhaps, the greatest vogue at present. According to this classification, cases of jaundice are divided into three groups: obstructive, toxic and infectious, and haemolytic. It is clear, however, that an haemolytic jaundice may be also a toxic (*e.g.*, phenylhydrazine poisoning) or an infectious (*e.g.*, Welch bacillus septicaemia) jaundice. Furthermore, into which of those catagories could one logically place the jaundice of heart failure? And, finally, the division "toxic and infectious" includes, for example, the jaundice occurring during lobar pneumonia as well as that occurring in yellow fever—types of jaundice which are ordinarily as widely divergent in their clinical and pathological manifestations as are the above-mentioned examples of acute yellow atrophy and congenital haemolytic jaundice. This classification of McNee's has undoubtedly served a useful purpose, for it was in certain respects an advance over former classifications; but it falls short in numerous points such as those which I have mentioned. An obvious weakness lies in the fact that, whereas the first and last divisions of this classification are based upon pathogenesis, the second division is based not upon pathogenesis but upon etiology. It is inevitable in such a scheme that a single form of jaundice will fall into more than one division.

On careful examination of the types of jaundice it became apparent that, in spite of the differences in the etiology and in the pathogenesis of different cases, all of the various forms could be divided into two distinct groups from the standpoint of both the clinical laboratory findings and the essential mechanism responsible for the jaundice. The first of these groups includes those cases in which the liver is functionally unable to free the blood from bilirubin produced in excess; the pigment is therefore retained in the body and stains the tissues. In the second group the jaundice is a result of the escape of whole bile from the canaliculi into the blood stream, either because of obstruction to the outflow through the ducts or because of necrosis of the liver cells. The first type I shall speak of as *retention jaundice*, because it involves merely an abnormal retention of pigment; the

second type I shall call *regurgitation* jaundice, because the characteristics result not from mere retention of pigment, but from regurgitation into the blood of pigment which has become mixed with other constituents of the bile in the bile canaliculi.

CHARACTERISTICS OF THE TWO MAIN TYPES OF JAUNDICE

Retention jaundice in its pure form, whatever the etiology, is recognizable clinically by the following characteristics: (1) the bilirubin of the plasma, never having passed through the liver cells and being, therefore, unmixed with the constituents of the bile, gives the indirect van den Bergh reaction; (2) the stools contain an increased amount of urobilin because, in the face of the increased production of bilirubin the liver is excreting more of the pigment than normally even though it cannot excrete enough of the excess to prevent jaundice; and (3) the urine contains an increased amount of urobilin but no bilirubin, for reasons discussed above; and it is free from bile salts because bile salts are formed in the liver and are absent from the urine unless they have been poured into the blood by the escape of whole bile from the canaliculi into the blood stream. Pathologically, the liver cells may show cloudy swelling, or atrophy, according to the etiological reason for their mal-function, but there is no widespread necrosis; and the bile-ducts are patent.

In the pure form of *regurgitation jaundice*, on the other hand (1), the plasma bilirubin gives the direct van den Bergh reaction because the bile canaliculi are altered in such a way that whole bile escapes into the blood stream; (2) the stools contain less urobilin than normally because the passage of bilirubin to the intestine is interfered with either by obstruction of the ducts or by necrosis associated with ruptures of canaliculi which allow the bile to leak into the blood stream; and (3) the urine contains bilirubin, since, for reasons discussed above, direct reacting plasma bilirubin escapes into the urine. Bile salts are usually present in the urine at some stage of the condition, because in this form of jaundice whole bile finds its way into the blood; and urobilinuria may also occur depending upon the balance between the amount of pigment reaching the intestine and the degree of damage to the liver. Pathologically, either the bile-ducts are obstructed or there is necrosis of the liver cells. The laboratory findings in regurgi-

tation jaundice are thus quite the reverse of those in retention jaundice, as the following table indicates (Table III).

Into these two main groups all of the various forms of jaundice can be rationally and helpfully placed from the standpoint of pathogenesis, for the results of the laboratory findings, as listed above, will enable one to determine the fundamental mechanism responsible for the jaundice in a given case and will permit one to form a judgment regarding the general type of anatomical alteration present in the liver. It must be borne in mind, however, that combined forms occur not infrequently. As an example, a pure retention jaundice may be present in association with heart failure because, as we shall see, anoxaemia causes atrophy and diminished excretory power of the liver cells and because there is commonly, in heart failure, an increased production of

TABLE III

The differences between the clinical laboratory findings in the two main types of jaundice

	BLOOD (VAN DEN BERGH REACTION)	URINE			FAECES (UROBILIN)
		Bilirubin	Bile salts	Urobilin	
Retention jaundice	Indirect	0	0	+	Increased
Regurgitation jaundice	Direct	+	+	0 +	Decreased

bilirubin. But long continued chronic passive congestion may produce not only atrophy of the liver cells with functional depression, but actual necrosis, often of widespread extent; and when this occurs, whole bile leaks back into the blood and a regurgitation jaundice becomes superimposed. The blood bilirubin changes from indirect to diphasic and finally becomes direct in reaction, and this, together with the pigment content of the stools and urine, allows one to recognize the development of the regurgitation jaundice and informs one that the damage to the liver cells has progressed from atrophy to necrosis.

We shall now turn to a discussion of the various subdivisions of these two main forms of jaundice.

I. RETENTION JAUNDICE

I A. *The rôle of anoxaemia.* The part played by anoxaemia in the production of certain forms of jaundice has only recently become recog-

nized. A number of years ago, I undertook a morphological study to determine whether or not in cases of pernicious anaemia any pathological change could be detected in the liver which might throw light upon its inability to excrete satisfactorily the increased amount of bilirubin produced in this disease. It soon became clear from a study of a series of cases that the cells about the efferent vein of each lobule were distinctly atrophied, often to a marked degree. In order to determine whether or not this lesion was peculiar to pernicious anaemia or whether it occurred in any severe anaemia, the livers from a long series of cases of secondary anaemia associated with a wide variety of conditions were examined. In these cases as well, atrophy of the central portion of each lobule was obvious, and the degree to which it was present was usually, but not invariably, proportional to the severity and duration of the anaemia. I have never seen this condition described as a characteristic effect of anaemia, although microphotographs and drawings of the liver in various publications dealing with other aspects of anaemia show the lesion plainly. Certainly, the major pathological treatises make no mention of it. They do state, of course, that fat droplets appear in the liver cells during severe anaemia, but the presence of fat droplets in the liver cells is so well known to occur under a variety of conditions which do not in any way, as far as can be determined, impair the function of the liver, that one could hardly regard the presence of fat alone as an indication of a depressed excretory power in anaemia. In the case of outspoken atrophy, however, one is obviously dealing with a lesion which must be associated with a lowering of the functions of the atrophied cells.

As to the cause of the atrophy, it seemed clear that, since it occurred in so wide a variety of pathological conditions associated with anaemia, it was probably a result of some factor common to all of those conditions. The most obvious factors common to the cases studied were (1) an insufficient number of oxygen-carrying blood cells and (2) diminution of food intake during the days preceding death. That prolonged fasting can bring about shrinkage of the liver cells is well known, and had to be considered, even though the amount of food taken during the final illness of the anaemic patients in the series studied was no less than that taken by other moribund patients without severe anaemia and without alteration of the liver cells. In

order to control the matter, however, several patients with severe anaemia were carefully fed a sufficient amount of nourishing food during their stay in the hospital up to the day of death. Their livers at autopsy, nevertheless, showed the usual well marked central atrophy noted in the other cases of anaemia in the series studied. Dr. Bumstead and I then set about to determine whether we could produce the lesion experimentally in dogs by simple haemorrhage. This we were able to do, and the location of the atrophy was the same as that observed in the patients with anaemia—*i.e.*, about the efferent vein of each lobule. Further suggestive evidence that the atrophy is a result of an insufficient oxygen content of the blood was the fact that in many of the cases of anaemia the shrinkage of the cells about the efferent veins was so marked that the consequent widening of the capillaries in the affected region produced the appearance characteristic of chronic passive congestion. Indeed, the protocols of some of the cases studied contain such statements as "the section of the liver has the appearance of chronic passive congestion" or "there is congestion in the central part of the lobules," although the heart in these cases was clinically and pathologically normal and there were no other evidences of chronic passive congestion, and no reason for its presence. Now although it is quite well known that chronic passive congestion produces atrophy of the central portion of the liver lobules, the reason for this atrophy has been a disputed point. Many have regarded it as a result of the pressure exerted by the dammed-back blood—a view which has long been opposed by MacCallum (16), and which, indeed, has little to recommend it when the facts are properly considered. The view supported by MacCallum is that the cells undergo atrophy because of an insufficient supply of oxygen. The fact that an exactly similar lesion accompanies both severe anaemia and chronic passive congestion appeared to us to be further suggestive evidence, at least, that the underlying cause of the atrophy in both of these conditions is the reduced oxygen supply. Shortly after attention had been called to this matter (17), Rosin mentioned a similar change in the liver in a description of the pathological effects of low barometric pressures (18), and, finally, by means of a specially constructed gas chamber (19), Dr. Bumstead, Dr. Barron and I were able to produce the lesion in dogs and in guinea-pigs by subjecting them to an atmosphere in which

the oxygen tension alone was reduced (21). While these latter experiments were in progress, Campbell (20), in a paper on the effects of low oxygen tension, pictured the same lesion in the liver which, however, he interpreted not as a direct effect of anoxaemia upon the liver, but as a result of a generalized chronic passive congestion resulting from heart failure. While it is true that one can produce a condition of heart failure by prolonged, severe anoxaemia, we have carried out experiments which demonstrated that atrophy and even necrosis of the central cells of the liver lobules will occur as a result of anoxaemia in the absence of heart failure and in the absence of any evidences of passive congestion in the lungs, spleen or other organs (21). It seems clear that anoxaemia specifically produces atrophy of the hepatic epithelial cells and that the cells about the efferent vein, in contrast to those in the periportal region, are definitely more sensitive to the effects of a deficient oxygen supply, just as they are well known to be more susceptible than the peripheral cells to the noxious effects of chloroform and certain other poisons.

Although it is hardly possible that shrunken, atrophic cells can function as efficiently as normal ones, it remained, nevertheless, to demonstrate that anoxaemia does depress the excretory function of the liver. In the case of the jaundice associated with pulmonary infarction during heart failure Rich and Resnik, following up various leads mentioned above, presented experimental evidence pointing to the rôle of anoxaemia in the depression of the excretory function of the liver (17). Keefer and Resnik subsequently attempted to show that anoxaemia could depress the excretory power of the liver and produce a bilirubinaemia in dogs poisoned the day before with carbontetrachloride, a drug which causes central necrosis of the liver (49). However, in agreement with the work of Lamson and his coworkers (48) who showed that simply because of the widespread death of liver cells caused by the poison, a rise of plasma bilirubin is to be expected during the day following the administration of carbontetrachloride, we found that if the experimental procedures of Keefer and Resnik were repeated precisely, without introducing the factor of anoxaemia, a comparable rise in plasma bilirubin ordinarily occurred during the same period of time as in their experiments with anoxaemia (21), and a more satisfactory method of studying the matter had to be devised.

Dr. Bumstead and I several years ago were able to obtain some evidence of impairment of the excretory power of the liver in anaemia, both in patients and in experimental animals, by studying the blood bilirubin curve following the intravenous injection of laked blood, and this depressed excretory function in anaemia has since been brought out more strikingly by the intravenous injection of pure bilirubin, a method of testing the excretory function of the liver, recently improved by Barron and Harrop (50). That a depressed excretory function is commonly an accompaniment of severe or prolonged anaemia seems clear from these studies; and by the use of the gas chamber referred to above we have been able to demonstrate that simple anoxaemia brings about not only the above described atrophic shrinkage of the liver cells, but that it also produces a concomitant depression of the ability of the liver to excrete bilirubin injected into the blood stream (21).

It is on the basis of these considerations that I have placed anoxaemia in the above classification as one of the causes of depressed liver function which, when associated with an increased production of bilirubin, leads to retention jaundice. As a support of what I have said at the outset regarding the necessity of a combination of both a depressed excretory function and an excessive production of bilirubin for the occurrence of retention jaundice, it may be remarked that, no matter how severe the atrophy of the liver cells may be in anaemia, jaundice never occurs unless there is at the same time a demonstrable over-production of bilirubin. Likewise, in our experimental animals, marked atrophy resulting from haemorrhage anaemia, or from sojourn in the gas chamber at low oxygen tension, never resulted in jaundice, and to demonstrate the impaired excretory power of the liver it was necessary to inject either bilirubin, or haemoglobin from which bilirubin is promptly produced, into the blood stream. This, as pointed out in the beginning of this paper, is a result of the great reserve excretory power of the liver, which allows one to remove all but a fraction of the normal liver substance without the production of jaundice if no more than the normal daily amount of bilirubin has to be excreted.

When the cells about the efferent vein of the liver lobule are reduced to a state of atrophy as a result of anoxaemia they appear to be much more susceptible to the effects of injurious agents than are normal

cells. In the study of human livers from cases of severe anaemia, a terminal, fresh, central necrosis of the atrophied cells was encountered not infrequently in association with terminal infections, and we have observed it likewise in some of our anaemic dogs which developed infections. However, a severe enough degree of anoxaemia can itself cause central necrosis, as is evident from the fact that some of our animals kept in the gas chamber at low oxygen tension for a week or more developed central necrosis in the absence of any detectable intercurrent infection, and death of this part of the liver lobule occurs in severe chronic passive congestion without infection. When necrosis of these cells is widespread enough, it is clear, from what has been said above, that the laboratory findings characteristic of regurgitation jaundice will make their appearance, for whole bile then leaks into the blood from the broken canaliculi in the necrotic area.

The two forms of retention jaundice which have their origin in the association of anoxaemic depression of liver function with increased bilirubin formation are (1) jaundice in the so-called "haemolytic" anaemias and (2) jaundice in cardiac decompensation.

I A_1. *Jaundice in anaemias associated with over-production of bilirubin.* No further discussion is required to indicate the reason for placing in this category the jaundice occurring in pernicious anaemia, haemolytic jaundice, sickle-cell anaemia, paroxysmal haemoglobinuria, mismatched transfusion in cases of anaemia, and the jaundice following massive red cell destruction by haemolytic poisons. The factor of anoxaemic depression of the excretory power of the liver resulting from anaemia is present in each of these conditions, and in each the increased pigment content of the blood, stools and urine is clear enough evidence of increased bilirubin production.

It may be pointed out that paroxysmal haemoglobinuria offers certain information in support of the view expressed in this paper that visible jaundice will rarely occur even in the presence of increased bilirubin formation unless the excretory capacity of the liver is diminished, and that anaemia can effect a lowering of the liver's excretory power. Following the attack of haemolysis brought about by exposure to cold, much of the haemoglobin liberated into the blood stream is converted into bilirubin, as can be determined by an examination of the pigment content of the blood, urine and stools. Jaundice,

however, by no means invariably occurs, and whether or not it does occur is not dependent simply upon the degree of haemolysis. Jaundice following an attack occurs more especially in patients who have been rendered anaemic by previous attacks, as can be seen from the following table of the cases on record in the Johns Hopkins Hospital (Table IV). There are uncontrolled factors in these clinical cases which interfere with any absolute conclusions, for the amount of blood destroyed in the attacks was not estimated, nor was the amount of unconverted haemoglobin lost in the urine determined. It is interesting, however, that it was in the cases with the fewest red cells available for destruction and therefore with a smaller available source of bilirubin (*i.e.*, cases with severe anaemia) that jaundice appeared.

TABLE IV

The relation of anaemia to the occurrence of jaundice in paroxysmal haemoglobinuria

CASE NUMBER	DIAGNOSIS	RED BLOOD CELLS	LOWEST HEMOGLOBIN	JAUNDICE FOLLOWING ATTACKS
			per cent	
26507	Paroxysmal haemoglobinuria	4,000,000	70	0
26471	Paroxysmal haemoglobinuria	5,400,000	74	0
33863	Paroxysmal haemoglobinuria	5,200,000	78	0
19426	Paroxysmal haemoglobinuria	792,000	17	+
30304	Paroxysmal haemoglobinuria	730,000	22	+

This is in agreement with our experiments referred to above in which patients and animals with severe anaemia showed a retention of bilirubin following the injection of laked blood. How well the observations in these unselected cases of paroxysmal haemoglobinuria may be supported by a larger series of cases I do not know. They are offered here as merely suggestive confirmatory evidence of the effect of anaemia upon the ability of the liver to excrete bilirubin.

I have said above that jaundice resulting from over-production of bilirubin in the absence of depressed liver function rarely if ever occurs, because of the great reserve excretory power of the liver and because bilirubin is, as far as we know, formed only from the haemoglobin of destroyed red cells, and therefore an excessive formation of bilirubin is associated with an excessive destruction of red cells and an attendant depressing effect of anaemia upon the liver. If it be

true that bilirubin can be formed from substances other than haemoglobin, it is, of course, possible to conceive of the abnormal production of an amount of the pigment greater than that which the normal liver, unaffected by anaemia, can excrete. However, there is no form of jaundice which requires this assumption, for a glance at the above classification will show that in each condition in which there is an over-production of bilirubin there are associated reasons for a depressed excretory power of the liver. It is true that occasional cases of congenital haemolytic jaundice have been reported in which the anaemia was slight in comparison with the degree of jaundice. I have never had an opportunity to test the excretory power of the liver for bilirubin in such a case but it would be important to do so, for it is entirely probable that a long continued chronic anaemia of relatively mild degree can bring about a lowering of the excretory power of the liver. Such cases are quite exceptional, however, and require further analysis. It may be that they represent instances in which an excessive red cell destruction is continually compensated by the vigorous regeneration of cells in the marrow, which is a characteristic of haemolytic jaundice. In hardly any other disease is the reticulocyte count so high. In this condition in which 10 per cent to 50 per cent of the red cells are reticulocytes, it is, furthermore, of importance to know whether cells of this character which, in contrast to mature red cells, demand an appreciable amount of oxygen for their own metabolism (22), are able to supply the tissues with oxygen as readily as are mature red cells. However, with very rare exceptions, cases of haemolytic jaundice are also cases with definite anaemia, and it is interesting to note that in going over the rather few autopsy protocols of this disease in the literature the morphological effects of anaemia upon the liver are usually found plainly described. Thus, Vaquez and Giroux (23), Vaquez and Ambertin (24), and Oettinger (25) describe atrophy of the liver cells, the last stressing the central location of the atrophied cells; Widal and Joltrain (26) and Strauss (27) describe central necrosis (I have mentioned above the not so infrequent terminal necrosis superimposed upon the atrophic central cells in anaemia); Gandy and Brulé (28), Wilson (29), and Tileston and Griffin (30) describe, in cases with no reason for chronic passive congestion, "congestion," "sinuses distended with blood," or "capillaries much

dilated"—descriptions which, as I have pointed out, have frequently been applied to the condition of the liver in anaemias in the protocols of this department, the widening of the capillaries (a necessary consequence of atrophy of the liver cells) having been misinterpreted as a primary congestion.

It is hardly necessary to point out that, since in any pathological condition which tends to produce anoxaemia there is usually an attempt on the part of the heart to compensate by sending more blood to the tissues, the degree to which the liver cells will be affected by anaemia will depend in part upon the degree to which the heart is able to compensate for the lowered oxygen-carrying power of the blood. The degree of liver damage, therefore, is not always directly proportional to the degree of anaemia.

I A_2. *Jaundice in cardiac decompensation.* In practically every case of outspoken chronic passive congestion associated with heart failure, an examination of the blood will show a bilirubin content higher than normal, even though the retention of pigment may not be sufficient to stain the skin and sclerae to a visible degree. The cause of this pigment retention lies in the following circumstances: (1) the excretory function of the liver is impaired by anoxaemia, and (2) the insufficient liver is called upon to excrete a larger amount of bile pigment than is formed normally. Pathologically, the atrophy of the central cells of the liver lobule is recognisable even on inspection of the gross organ (the familiar 'nutmeg liver'); and that there is actually an increased production of bilirubin is evident from the presence of an increased amount of this pigment in the blood, coupled with an increased amount of urobilin in the stools and urine.

Not infrequently the pigment retention in chronic passive congestion is intensified to the point that a distinct scleral or even cutaneous jaundice becomes obvious. Any increase in the degree of anoxaemia during cardiac decompensation reduces still further the excretory power of the liver and so increases the pigment retention, and this is especially striking when a patient with heart failure develops a pulmonary infarct. Eppinger (31), ten years ago, drew especial attention to the fact that the sudden appearance of jaundice during heart failure is almost always the result of pulmonary infarction. He believed that the haemorrhagic infarction of the lung led to jaundice

because it provided a source of locally formed bilirubin, or of haemoglobin from which bilirubin could be made. Rich and Resnik (17), however, showed that when amounts of blood equal to that in pulmonary infarcts accompanied by jaundice were injected into the tissues of patients with cardiac decompensation, not only did jaundice fail to appear, but there was not even a significant rise of the blood bilirubin following the injections. It was suggested at that time that the increased inability of the liver to excrete bilirubin following pulmonary infarction in heart failure is a result of the intensification of anoxaemia which Binger, Brow and Branch had shown to follow pulmonary infarction (32). That view has since been substantiated by the experiments of Rich, Bumstead and Barron which demonstrated the depressive effect of anoxaemia upon the excretory power of the liver (21).

The occurrence of jaundice following pulmonary infarction in heart failure supports, to a certain extent, the view put forth at the beginning of this paper, that jaundice occurring in the absence of obstruction or of necrosis of liver cells ordinarily requires two factors—a decreased excretory power of the liver and an increased production of bilirubin; for pulmonary infarction occurring in conditions in which there is no increased production of bilirubin (*e.g.*, following surgical operations) does not lead to jaundice although it does create a condition of anoxaemia, as Binger, Brow and Branch have shown (32). Furthermore, the fact that bilirubin excretion suffers an immediate impairment following pulmonary infarction in heart failure is clinical evidence that anoxaemia tends to depress the excretory power of the liver.

The anatomical liver damage in chronic passive congestion may be, and in all except severe cases is, confined to atrophy of the central cells of each lobule. When jaundice occurs under this condition, it is a pure retention jaundice. In severe and protracted cases of chronic passive congestion, however, or in cases complicated by pulmonary infarction, actual necrosis of the central cells not infrequently occurs. When this happens to a marked enough degree, the characteristics of regurgitation jaundice naturally make their appearance, *i.e.*, the reaction of the plasma bilirubin changes from indirect through the diphasic stage to direct, and bilirubin and even bile acids appear in the urine.

I B. *Jaundice in febrile disease associated with anoxaemia and overproduction of bilirubin.* It is well known that during febrile states there commonly occurs a morphological alteration of the epithelial cells of various organs which formerly was termed "parenchymatous degeneration" but which is now perhaps more generally known as "cloudy swelling." This lesion involves the epithelial cells of the liver and kidneys so commonly during fever, and is now so well known to be only a temporary change from which complete recovery takes place when the causal febrile condition has disappeared that, in contrast to the importance which was attached to the striking alteration of cell structure a number of years ago, parenchymatous degeneration today hardly receives passing attention. The presence of cloudy swelling makes it clear that during many febrile diseases the metabolism of the parenchymatous cells of various organs is definitely altered in some way; but to what degree this sign of an internal abnormality can be regarded as an indication of a disturbance of the specific functions of the affected cells is another matter. Certainly in the case of the kidney, aside from the presence of albumin and casts in the urine no very marked disturbances of function are associated with cloudy swelling. Somewhat less attention has been paid to the effects of febrile disease upon the various functions of the liver, and there are few experiments on record bearing upon the matter. It is of importance that this question be studied in animals or in patients with bile fistulae. However, scattered observations indicate that various functions of the liver may be disturbed during fever. McMaster, Broun and Rous (33), for example, describe a marked reduction in the total quantity of bile excreted by dogs during intercurrent infections; and in the one dog in which figures for the excretion of bilirubin are given, the 24-hour output of pigment during a respiratory infection was about half that of the normal animal. Ottenberg, Rosenfeld and Goldsmith (34) report a delayed hepatic excretion of tetrachlorphthalein during lobar pneumonia, and Cohen and Levin (35) state that the formation of urea was subnormal in three out of four cases of pneumonia which they studied. Indeed, the common occurrence of urobilinuria during fever has, on the basis of what is known of the relation of disturbed liver function to urobilinuria, long been regarded as evidence of disturbed hepatic function during febrile states. The morphological

alteration of parenchymatous degeneration coupled with the available suggestive evidence of functional impairment of the liver during fever requires that provisionally, at least, we regard febrile disease as a possible factor in depressing certain functions of the liver. This does not imply, of course, that it is the elevation of temperature in itself which is chiefly responsible for such functional disturbances as may exist. On the contrary, it is more probable that the cells are damaged by products of the infecting organism responsible for the febrile state. That febrile disease and cloudy swelling in themselves are insufficient to depress the excretory power of the liver to the point that jaundice will appear must be obvious from the fact that these factors in their most aggravated form (*e.g.*, typhoid fever) fail to cause jaundice unless other predisposing factors are added. The other predisposing factors ordinarily associated with jaundice in febrile diseases are (1) over-production of bilirubin, and (2) anoxaemia.

It is necessary to regard the marked inspissation of the bile which may occur during infections (33) as a possible accessory factor in rendering difficult the free passage of bile through the canaliculi. This was, in fact, the essence of Eppinger's "bile thrombi" teaching, but the absence of histological evidence of extensive plugging of canaliculi by inspissated bile in most cases of retention jaundice, coupled with the fact that an icterus resulting from obstruction of the canaliculi with rupture of their walls in the regions behind the plugs must have the clinical manifestations of regurgitation jaundice, prevents the acceptance of this factor as the explanation of many of the forms of retention jaundice to which Eppinger originally applied it. There are, undoubtedly, instances of febrile infections associated with increased red-cell destruction in which one finds many canaliculi distended with bile at autopsy, but one cannot at once accept these distended canaliculi as being plugged with bile thrombi. It is interesting that such distended canaliculi are ordinarily found in the central part of the lobule about the efferent vein—a fact which suggests a relationship to a zonal damage of liver cells rather than to obstruction because of a general inspissation of the bile. It is possible, it seems to me, that the accumulation of bile in these centrally situated canaliculi may be merely a result of the depression of function of the central cells to the point that they are unable to excrete and force the bile under pressure

through the canaliculi. The continued excretion of the less damaged peripheral cells would under such a circumstance cause the bile to flow backward into and to fill up the central canaliculi, on the contents of which no forward-propelling force would be exerted by the related damaged cells. As a matter of fact just this over-filling of the central canaliculi can often be seen in cases in which a poison or chronic passive congestion has damaged specifically the central cells.

I B_1. *Jaundice in febrile haemolytic anaemias.* If, to a liver with its function disturbed by febrile disease, there is delivered for excretion an excessive quantity of bilirubin, the amount retained in the blood might rise to a level capable of producing outspoken jaundice. There is evidence, however, that even though it may be depressed during fever, the excretory power of the liver may nevertheless suffice to prevent jaundice even in the face of rather considerable increases in bilirubin production. Malaria provides evidence in this direction, for in spite of the liberation of rather large amounts of haemoglobin into the blood stream during the periodic destruction of red cells, jaundice does not occur during the early stages of the disease, although the bilirubin content of the plasma rises above normal during each febrile attack. Later in the disease, however, when to the effect of the fever there is added the depressing effect of severe anaemia, the liver may be rendered insufficient to excrete the excess of bilirubin, and jaundice may appear. Klotz (36) has pointed out that, in severe cases of malaria with jaundice, necrosis of the hepatic cells may be encountered, and the effect of this in assisting the development and intensification of jaundice (and incidentally in transforming a retention jaundice into a regurgitation jaundice) is obvious.

A similar state of affairs obtains in the haemolytic septicaemias, for in addition to whatever depressing effect the febrile infection exerts upon the excretory power of the liver, there must also be taken into account the effect of the anaemia resulting from the destruction of red blood cells, and the fact that an excess of bilirubin is produced from the haemoglobin of the destroyed cells.

I B_2. *Jaundice in lobar pneumonia.* The cause of the jaundice which occurs not infrequently during lobar pneumonia has long been obscure, and numerous theories have been advanced to explain it. It is often stated that the jaundice is a result of a "toxic hepatitis"

produced by the pneumococcal infection. An obvious objection to this statement is the fact that jaundice is not observed in the face of severe pneumococcal infections in locations other than the lungs (not in the peritoneum or the meninges, for example). Indeed a careful study of a series of livers from cases of pneumonia with jaundice will make it evident to any observer that no inflammatory lesion of the nature of a hepatitis is present. As for the inflammation of the bile passages which is also given as a cause of the jaundice, I have never seen a recognizable inflammation of the bile ducts (cholangeitis) in any of the numerous cases of pneumonia with jaundice which I have had an opportunity to study. Regarding the "inflammation of the bile *canaliculi*" which some writers assume to be present, that is a somewhat theoretical state which hardly occurs under any circumstances. Herzfeld and Steiger (44) believed they had demonstrated that the pneumococcus could produce bilirubin from haemoglobin, and on this basis McPhedran (45) and others have attributed the jaundice to the formation of bilirubin from the haemoglobin of the red cells of the pneumonic exudate. Rich and Bumstead (46), however, were unable to confirm Herzfeld and Steiger's report of the power of the pneumococcus to convert haemoglobin into bile pigment, and demonstrated by more delicate tests that the anomalous Gmelin reaction observed by Herzfeld and Steiger was produced by a substance which was not bilirubin. Furthermore, one could cite, as an argument against the idea of the production of jaundice by absorption of locally formed bilirubin, such cases as that described by Rich and Bumstead, in which a vascular, thin-walled, peritoneal cyst containing several litres of a haemorrhagic fluid, with a bilirubin content approaching that of gall-bladder bile, failed to cause any elevation of the bilirubin content of the patient's plasma (47). Indeed, the experiments of Rich and Resnik (17), which demonstrated that the absorption of pigment from artificially produced haemorrhages of considerable size fails to cause an elevation of blood bilirubin even in patients with livers damaged by chronic passive congestion, argue against the mere absorption of pigment from the extravasated red cells in the lung as constituting the cause of the jaundice. As a matter of fact, when patients with lobar pneumonia accompanied by jaundice come to autopsy, the consolidation is found to be well on in the stage of gray hepatization and very few red cells can be found in the exudate.

Examined in the light of the facts already discussed in this paper, it becomes evident that in lobar pneumonia there are present, often in marked degree, two factors which may act to depress the function of the liver, namely, febrile infection and anoxaemia. I have referred to work indicating that the excretory power of the liver is impaired during pneumonia (34). There is, in addition, some evidence that an excess of bilirubin is produced in severe cases of pneumonia, for the stools have been found to contain more urobilin than normally (31). Dr. Hugh Josephs, of the Department of Pediatrics of this University, is at present making a careful study of the bile pigment metabolism during pneumonia, and he informs me that during the course of pneumonia he has observed increases of 100 per cent. above the normal quantity of urobilin excreted in the stools. From these considerations it seems proper to regard the occurrence of jaundice in pneumonia as a result of an over-production of bilirubin occurring in the face of a liver damaged by febrile infection and anoxaemia.

Occasionally, the laboratory findings characteristic of regurgitation jaundice make their appearance during the course of a severe retention jaundice in lobar pneumonia. In several such cases I have found at autopsy necrosis of liver cells, providing a means of escape of whole bile from canaliculi into the blood stream. The necrosis has in no case attacked large numbers of cells at any one point. On the contrary, single or at most a group of several cells have been affected at each site, but the distribution of necrotic cells has been widespread throughout the organ. I have seen the same type of necrosis (usually preceded by the appearance of hyalinized masses of protoplasm within the cells) in haemolytic septicaemias accompanied by jaundice of the regurgitation type, although in the latter infections more extensive foci of necrosis involving larger groups of cells are more commonly encountered in association with regurgitation jaundice. That small foci of necrosis are not sufficient to cause jaundice unless there is a concomitant overproduction of bilirubin is clear from the failure of jaundice to occur in cases of typhoid fever in which small foci of necrosis are abundant.

I C. *Icterus neonatorum.* The plasma of the normal infant at the time of birth has a bilirubin content considerably higher than that which is normal for an infant several weeks old, or for an adult—so much higher, in fact, that if blood is taken from the umbilical cord

and, simultaneously, from a vein of the mother, the infant's plasma after centrifugalization can usually be distinguished from the mother's at a glance by reason of its deeper yellow color. In the majority of infants the amount of plasma bilirubin increases during the first few days of life to the level at which cutaneous jaundice becomes apparent. This is the so-called "jaundice of the new-born"—ordinarily a transient condition, and one which is to be regarded not as a symptom of disease, but rather as a manifestation of a physiological adjustment. Many theories have been proposed to explain this form of jaundice, of which Eppinger writes in his well-known monograph on jaundice: "I cannot say that we understand the matter clearly at present. Numerous important observations have been made, but up to the present there exists no single conception of the pathogenesis of icterus neonatorum which can be accepted" (40). Since, pathologically, there is no necrosis, obstruction, or rupture of canaliculi, and, since the icterus has the clinical characteristics of a retention jaundice, we may properly inquire whether the two factors—increased bilirubin production and subnormal liver function—which I have emphasized as underlying causes of most, if not all, cases of retention jaundice, are to be found in icterus neonatorum.

Regarding an increased production of bilirubin, it appears quite clear that this factor exists in the new-born. It is well known that the haemoglobin content of the blood at birth is above normal, and that a frank polycythaemia is often present. During the first few days after birth (the period in which icterus neonatorum appears) there occurs a rapid fall in haemoglobin, and any existing polycythaemia disappears. Simultaneously, the bilirubin content of the blood rises, bilirubin is present in abundance in the duodenal contents (39) and one can reasonably conclude that there has occurred an overproduction of bilirubin as a result of the rapid destruction of the excess of haemoglobin present in the circulation at the time of birth. There is also evidence that the excretory power of the liver is subnormal during the first few days after birth, for the organ is unable to excrete properly the various dyes used to test its excretory function (37) (38). This deficient excretory power appears to be simply the result of immaturity, for the normal excretory power is soon developed, and furthermore, icterus neonatorum is especially common in prema-

ture infants. From these considerations I think that icterus neonatorum, like other forms of retention jaundice, can properly be regarded as the result of the fact that an excessive amount of bilirubin is delivered for excretion to a liver with a subnormal excretory capacity.

I D. *Hanot's cirrhosis.* That there exists a clinical condition such as that described by Hanot (jaundice, enlarged liver, no ascites) there can be no doubt, but whether or not it represents a simple entity or a symptom-complex common to a number of different pathological conditions no one can say at present, for the number of cases requiring this diagnosis is not large and too few have been carefully studied pathologically. Certainly, the type of cirrhosis ordinarily described in textbooks of pathology as characteristic of Hanot's cirrhosis is even more rarely encountered at autopsy than are the symptoms in the clinic. I have recently had an opportunity to examine microscopically a small piece of liver taken during life from a clinically typical case of Hanot's cirrhosis. It showed no scarring, but there were focal accumulations of mononuclear and polymorphonuclear cells about vacuolated and occasionally necrotic liver cells—a curious sort of sub-acute hepatititis which, it is conceivable, might have progressed in time to the state of fine, diffuse scarring described by Hanot. I have placed Hanot's cirrhosis among the forms of retention jaundice for the reason that in several cases studied rather carefully clinically (no autopsies) the laboratory findings were those characteristic of retention jaundice. This classification of Hanot's cirrhosis is, however, a purely tentative one, and a final classification must await a better clinical and pathological study of the condition.

II. REGURGITATION JAUNDICE

II A 1. *Jaundice resulting from the rupture of canaliculi caused by toxic agents.* There are various chemical, bacterial and vegetable poisons which possess the property of producing damage and death of the hepatic cells. The localized zonal damage produced by many of these injurious agents should certainly direct attention to the possibility that the liver cells situated in different parts of the lobule, although apparently all quite alike morphologically, may actually be quite different functionally. At least their internal contents must be different or else it is hardly conceivable that different poisons would

invariably attack different portions of the lobule with such striking specificity. Chloroform, carbon tetrachloride and arsphenamin, for example, produce central necrosis with perfect regularity unless the dose is large enough to damage the entire lobule, and I have discussed the sensitivity of this portion of the lobule to the effects of anoxaemia; the products of the virus of yellow fever and of certain other infectious agents attack primarily the midzonal portion of the lobule; and the periportal region is specifically affected in eclampsia. The sharp zonal accumulation of fat which is so frequently and so brilliantly seen at autopsy is further evidence of zonal differences in metabolism. It has been suggested that in chronic passive congestion the central cells die because the oxygen content of the blood is low and the periportal cells, having the first chance at the available oxygen, leave too little in the sinusoids to nourish the central cells. If the explanation were as simple as that, chloroform, for example, should produce periportal necrosis, for it is the periportal cells which are first exposed to it. It seems much more probable that the difference in susceptibility of the cells in the different portions of the lobule to a given noxious accident is a result rather of specific internal differences in the constitution and function of the cells. More pointed histochemical studies may very possibly disclose a division of functions between these cells which appear so exactly similar, morphologically, in ordinary histological preparations.

Under different conditions of metabolism the cells may exhibit strikingly different degrees of susceptibility to the same poison. It is well known, for example, that by diet regulation the central cells can be rendered more susceptible or more resistant to the necrotizing effect of chloroform or carbon tetrachloride (Whipple; Lamson). Since this is the case, it seemed worthwhile to test the effect of diet in preventing the all too frequent and serious liver damage accompanied by jaundice which occurs during the treatment of syphilis with salvarsan. Dr. Craven has recently completed a study of this question in our laboratory, and he has demonstrated that, in dogs, a high carbohydrate diet strongly predisposes to the liver damage caused by this drug, whereas a high fat diet confers a marked degree of protection against it—a condition of affairs exactly the reverse from that which obtains in chloroform or carbon tetrachloride poisoning, although the cells affected are the same (central).

There is no difficulty in understanding the mechanism of the regurgitation jaundice which results from a widespread destruction of liver cells by any of the various toxic agents which specifically kill these cells. Figure 1 shows, in a schematic way, the manner in which whole bile is regurgitated into the blood stream under such circumstances.

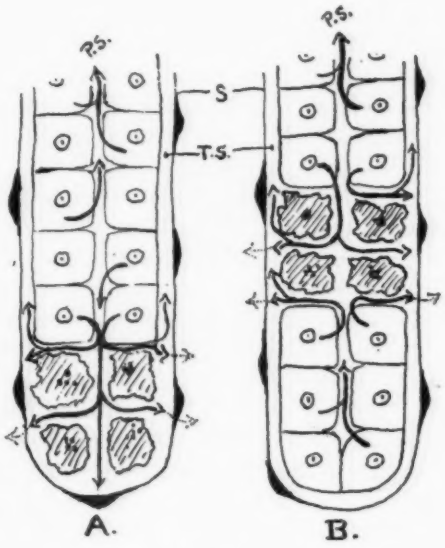

FIG. 1

T.S. = tissue space; S. = Endothelial lining of sinusoid; P.S. = Direction of bile duct in periportal space. The arrows indicate the manner in which bile is regurgitated into the tissue spaces and blood stream when the canaliculi are ruptured as a result of necrosis of the hepatic cells. A shows the condition in central necrosis, B in midzonal necrosis.

Because of the great reserve excretory power of the liver it requires the death of a very considerable amount of the organ to precipitate jaundice in the absence of increased bilirubin formation. Jaundice, for example, is very rare in typhoid fever, as I have said, although each microscopic section taken at random in the liver may show numerous foci of necrosis. In conditions in which more extensive necrosis occurs,

however, jaundice makes its appearance even in the absence of increased bilirubin production, for it is to be remembered that under such circumstances the reserve power of the liver, already decreased by the loss of many cells, and by the damage of many which are not killed outright, is working under a still further disadvantage in its effort to prevent jaundice, for in addition to the normal, daily amount of bilirubin, there must be excreted bilirubin which is constantly leaking back on all sides into the blood from the ruptured canaliculi.

The jaundice occasionally occurring in *Laennec's cirrhosis* requires perhaps, a special comment. Marked jaundice is uncommon in this disease, even in cases in which there has occurred a very great loss of liver tissue. The mildness or complete absence of jaundice is attributable to the gradual progress of the disease and to the considerable reserve excretory power of the liver. When great numbers of liver cells are killed suddenly by any poison, jaundice appears because the liver cells which remain cannot properly rid the blood of both the amount of bilirubin produced and the amount which leaks back into the blood stream from the ruptured canaliculi; but in Laennec's cirrhosis the death of liver cells proceeds so gradually, a few being killed here and a few there, that it is difficult even to find necrotic cells in sections from most cases and there is, therefore, usually enough liver tissue left intact in the early stages to prevent jaundice. As the disease progresses, a compensatory hyperplasia of liver cells proceeds side by side with the destructive process, and the connections of bile canaliculi which are interrupted by necrosis of the cells which form their walls are promptly repaired by regeneration of liver cells, and by the establishment of new connections with proliferating bile-ducts. It sometimes happens, however, that during the course of the disease, especially in the terminal stages, there occurs a period of more rapid and widespread destruction of cells, and in this event jaundice may make its appearance. I have seen such cases in which, in contrast to the usual difficulty of finding necrotic foci in a cirrhotic liver, such foci were present in abundance. This event reminds one very much of the occurrence of "acute exacerbations" during the course of a chronic, slowly progressing nephritis. Aside from such a period of intensified destruction of liver cells as a cause of jaundice in cirrhosis, it is also clear that,

because of the loss of liver substance, the reserve excretory power of a cirrhotic liver is considerably reduced; and that, therefore, if the disease happens to become complicated by any of the factors which we have discussed as having a tendency to cause jaundice, icterus will be precipitated much more readily in such an individual than in a person with a normal liver.

II B. *Jaundice caused by obstruction of the bile ducts.* The bile-ducts may be completely or partially obstructed (1) by abnormal material which plugs the lumen, (2) by changes in the wall of the duct leading to the formation of a stricture, and (3) by adjacent abnormal masses which compress the duct. Because of the reserve excretory power of the liver, jaundice does not as a rule result from obstruction unless the flow through the major part of the duct system is prevented. I have mentioned above a case which demonstrated that a main branch of the hepatic duct may be obstructed without the occurrence of jaundice.

The studies carried out in our laboratory by Bloom (41) and by Barron and Bumstead (42) have shown that for a period of time following acute obstruction of the common duct the bilirubin, gradually increasing in amount in the blood, gives only the indirect van den Bergh reaction; later the reaction takes the direct form characteristic of regurgitation jaundice. This is an indication that, in the early hours following the obstruction, the pigment which is accumulating in the blood is bilirubin which has not passed through the liver cells; it seems therefore probable that, for a while following acute obstruction, the excretory function of the liver cells may shut down in a manner comparable to that familiar in the case of the kidney cells in the 'reflex anuria' which sometimes follows mechanical irritation of the ureter. The cells soon resume their function, however, and bilirubin is excreted into the obstructed system until ducts and canaliculi are overfilled with bile. The distended canaliculi increase in size until their bulbous terminations extend into direct contact with the perivascular lymph space (Fig. 2), and when this occurs the plasma bilirubin gives the direct reaction even before rupture of the canaliculi can be demonstrated. The bile, under pressure because of the obstruction, apparently passes first into the adjacent lymph space by diffusion through the tenuous membranes of the distended ends of the canaliculi. That

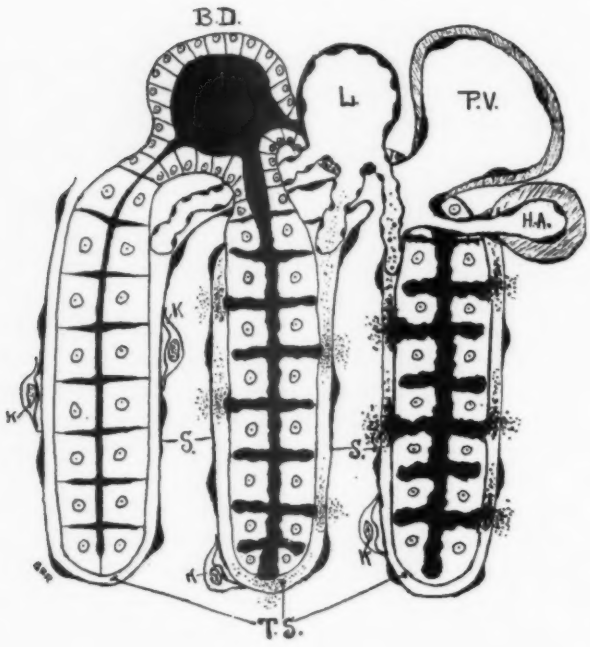

FIG. 2

B.D. = bile duct; L. = lymph vessel; P.V. = portal vein; H.A. = hepatic artery; T.S. = tissue space. S. = Endothelial lining of sinusoid. It will be noted that, contrary to text-book tradition, this endothelial lining is complete, and is formed of endothelial cells, not of the irregularly scattered Kupffer cells (K) as is often stated. Normally, the endothelium lies close against the liver cells, so that it is difficult or impossible to see it, but when the liver cells are atrophic (*e.g.*, in chronic passive congestion) they tend to shrink away from the endothelium, and the complete lining of the sinusoids often becomes beautifully clear. The fact that in early obstructive jaundice bile pigment appears in the lymph earlier than in the blood stream is itself evidence that the tissue space is separated from the blood by a complete lining.

The cord of liver cells on the left in the diagram illustrates the normal relations of the bile canaliculi (tissue space exaggerated). The cord of cells in the center illustrates the distension of overfilled canaliculi (*e.g.*, early stage of obstructive jaundice) until bulbous ends project into the tissue space, and bile diffuses into that space and thence passes into the periportal lymphatic, with only slight diffusion into the blood through the endothelium of the sinusoid. The cord of cells on the right illustrates the conditions in established obstructive jaundice. Canaliculi are ruptured, and bile is emptied in large amounts into the tissue space, passing thence into the lymphatic and also diffusing through the sinusoidal endothelium into the blood stream.

the bile from the canaliculi enters the lymph space before it enters the blood is borne out by the fact that, as shown by Barron and Bumstead (42), and more recently confirmed by Mayo and Green (43), direct reacting bilirubin appears in the lymph before it is found in the blood stream following acute obstruction of the common duct. As the pressure rises in the canaliculi because of the continued discharge of bile into the obstructed system, many of the canaliculi actually burst, and whole bile regurgitates freely into the lymph space and passes eventually into the blood stream through walls of the hepatic capillaries and by way of the thoracic duct as well (Fig. 2). The clinical laboratory findings are those which I have outlined as characteristic of regurgitation jaundice (direct reacting plasma bilirubin, decreased amount of faecal urobilin, presence of bilirubin and, at some stage, of bile acids in the urine). It is hardly necessary to discuss separately the various causes of duct obstruction. The major ones are listed in Table II.

II C. *Catarrhal jaundice.* Catarrhal jaundice is a form of regurgitation jaundice of uncertain pathogenesis. The scanty literature dealing with the pathological changes in the liver associated with this rather common but non-fatal malady hardly allows one to speak with confidence about the matter, and I, myself, have had no first-hand experience with the disease at the autopsy table. In the records of the 11,500 autopsies which have been performed in this department during the past forty years there is not a single case in which the diagnosis of catarrhal jaundice could be regarded as accurate. Indeed, in only one case was this diagnosis even suggested. For a description of dilated and ruptured canaliculi, and of damage to the hepatic cells in catarrhal jaundice, one may turn to the protocols of cases regarded by Eppinger as catarrhal jaundice (40). Whatever may be the exact pathogenesis of this condition (which, indeed, probably represents a *mélange* of types of benign icterus of different etiologies), the clinical laboratory findings are unmistakably those of regurgitation jaundice. There is direct reacting bilirubin in the blood, decreased faecal urobilin, and bilirubin and even bile acids in the urine. This indicates clearly that, either because of obstruction of the ducts or because of necrosis of liver cells, whole bile is escaping from the canaliculi into the blood stream, and I have therefore placed this

disease under the heading of regurgitation jaundice while leaving the exact cause of the rupture of the canaliculi an open question.

SUMMARY

In this paper the various forms of jaundice are considered in the light of our present information regarding the physiology and pathology of the formation and excretion of bile pigment. It is pointed out that, from the standpoint of the clinical and pathological evidence, cases of jaundice are separable, on the basis of pathogenesis, into two main types.

The first type, *retention jaundice*, results from an over-production of bile pigment, usually associated with conditions (anoxaemia, fever, immaturity) which tend to render the excretory power of the liver subnormal; enough bilirubin is therefore retained in the blood to stain the tissues. This form of jaundice is characterized clinically by (1) indirect-reacting plasma bilirubin; (2) increased amounts of faecal urobilin; and (3) urobilinuria. Pathologically, the ducts are patent, but the liver cells may show atrophy or cloudy swelling, depending upon the associated condition of which the jaundice is a symptom.

The second type, *regurgitation jaundice*, is caused by the reflux of whole bile from the canaliculi into the blood stream. This type is characterized clinically by (1) direct-reacting plasma bilirubin (2) subnormal amounts of faecal urobilin, and (3) the presence of bilirubin and bile salts in the urine. The pathological basis of this form of jaundice is rupture of the canaliculi resulting from obstruction of the ducts or from necrosis of the hepatic cells.

Combined forms may occur, as well as a transition from one of these types of jaundice to the other.

A classification is offered in which the two types (retention jaundice and regurgitation jaundice) are further subdivided from the standpoint of etiology and pathogenesis, and the reasons for the various subdivisions are discussed.

REFERENCES

(1) MANN *et al: Am. Jour. Physiol.*, 1924, lxix, 393.
(2) RICH: *Bull. Johns Hopkins Hosp.*, 1925, **36**, 233.
(3) MAKINO: *Ziegler's Beitr.*, 1924, lxxii, 808.
(4) MANN *et al: Am. Jour. Physiol.*, 1926, lxxviii, 384.
(5) RICH AND RIENHOFF: *Bull. Johns Hopkins Hosp.*, 1925, **36**, 431.

(6) McNee: *Jour. Path. and Bact.*, 1913, xviii, 325.
(7) Rich: *Bull. Johns Hopkins Hosp.*, 1924, **35**, 415.
(8) Whipple: *Am. Jour. Physiol.*, 1926, **78**, 675.
(9) Rich: *Physiol. Rev.*, 1925, v, 182.
(10) Rich and Bumstead: *Bull. Johns Hopkins Hosp.*, 1925, **36**, 437.
(11) McMaster and Elman: *Jour. Exp. Med.*, 1925, **41**, 719.
(12) McMaster and Rous: *Ibid.*, 1921, **33**, 731.
(13) Van den Bergh: Der Gallenfarbstoff im Blute, Leipzig, 1928.
(14) Barron: *In press.*
(15) McNee: *Quart. Jour. Med.*, 1923, xvi, 390.
(16) MacCallum: Textbook of Pathology, W. B. Saunders Co., 1928, 469.
(17) Rich and Resnik: *Bull. Johns Hopkins Hosp.*, 1926, **38**, 75.
(18) Rosin: *Ziegler's Beitr.*, 1928, **80**, 662.
(19) Pierce: *To be published.*
(20) Campbell: *Lancet*, 1928, **2**, 84.
(21) Rich, Bumstead and Barron: *To be published.*
(22) Harrop: *Arch. Int. Med.*, 1919, **23**, 745.
(23) Vaquez and Giroux: *Bull. et mém. Soc. méd. des hôp.*, 1907, **24**, 1184.
(24) Vaquez and Ambertin: *Arch. d. mal. du coeur*, 1908, **1**, 609.
(25) Oettinger: *Bull. et mém. Soc. méd. des hôp.*, 1908, **26**, 391.
(26) Widal and Joltrain: *Ibid.*, 1908, **26**, 468.
(27) Strauss: *Berl. klin. Woch.*, 1908, **45**, 1643.
(28) Gandy and Brulé: *Bull. et mém. Soc. méd. des hôp.*, 1909, **29**, 369.
(29) Wilson: *Trans. Clin. Soc. London*, 1893, **26**, 163.
(30) Tileston and Griffin: *Am. Jour. Med. Sc.*, 1910, **139**, 847.
(31) Eppinger: Die Hepatolienalen Krankheiten, Berlin, 1920.
(32) Binger, Brow and Branch: *Jour. Clin. Investig.*, 1924, **1**, 127 and 155.
(33) McMaster, Broun and Rous: *Jour. Exp. Med.*, 1923, **37**, 395.
(34) Ottenberg, Rosenfeld and Goldsmith: *Arch. Int. Med.*, 1924, **34**, 206.
(35) Cohen and Levin: *Ibid.*, 1927, **39**, 787.
(36) Klotz: *Am. Jour. Trop. Med.*, 1929, ix, 241.
(37) Herlitz: *Acta Ped.*, 1926–7, vi, 214.
(38) Aballi, Angel and Castellanos: cited by Herlitz (ref. 37 above).
(39) Hess: *Am. Jour. Dis. Child.*, 1912, 304.
(40) Eppinger: Allg. u. spezielle Pathologie des Ikterus, Kraus-Brugsch Pathol. u. Therap., vi, 2.
(41) Bloom: *Bull. Johns Hopkins Hosp.*, 1923, **34**, 316.
(42) Barron and Bumstead: *Jour. Exp. Med.*, 1928, **47**, 999.
(43) Mayo and Green: *Am. Jour. Physiol.*, 1929, **89**, 280.
(44) Herzfeld and Steiger: *Med. Klin.*, 1910, vi, 1415.
(45) McPhedran: *Bull. Johns Hopkins Hosp.*, 1911, **22**, 408.
(46) Rich and Bumstead: *Bull. Johns Hopkins Hosp.*, 1925, **36**, 376.
(47) Rich and Bumstead: *Ibid.*, 1925, **36**, 225.
(48) Lamson, Gardner, *et al: Jour. Pharm. and Exp. Therap.*, 1923, xxii, 215.
(49) Keefer and Resnik: *Jour. Clin. Investig.*, 1925–6, ii, 389.
(50) Barron and Harrop: *To be published. Jour. Clin. Investig., Feb., 1931.*

CERVICAL ADENITIS DUE TO BACILLUS FUSIFORMIS

W. M. FIROR, M.D.

From the Department of Surgery, The Johns Hopkins Medical School and Hospital, Baltimore, Maryland

A year ago there was in the Johns Hopkins Hospital a patient whose illness evoked considerable discussion both as to the diagnosis and the appropriate therapy. This report of the case is being made not merely because of the interesting differential diagnosis nor because of the unusual etiological factor, but rather because it seems certain that there are similar cases which pass unrecognized. An abstract of the case follows.

CASE REPORT

The patient was a four-year-old girl who had always had the best medical care. She had had measles and occasionally acute pharyngitis. At two she was sick for three weeks with cervical adenitis that required drainage. A tonsillectomy was performed when she was three years old.

The illness which brought her to the hospital had begun four months before admission with an upper respiratory tract infection of two weeks' duration. During this time her temperature had varied from 100° to 104°F. After an interval of two weeks there was a recurrence of the infection, following which she had stertorous breathing, which a laryngoscopic examination failed to explain. Soon thereafter an attendant noticed an enlarged cervical gland on the left side. This gland increased rapidly in size and suggested an acute adenitis of pyogenic origin. When incised, however, the gland contained practically no pus. The drainage from the incision, although small in amount, persisted for two months. The tissues around the sinus became exceedingly hard. The cervical glands on the right side began to enlarge. A white blood count was so excessively high that the diagnosis of leukemia was made. During this illness of four months the patient lost four pounds in weight.

On admission to the hospital the child did not appear to be acutely ill. She was well nourished. Her temperature ranged from 98° to 100.4°; her respiratory rate was from 32 to 44; and her pulse varied from 120 to 140. Her breathing was easily audible throughout the room. The pharynx was not injected. The

tonsils had been entirely removed. On either side of the neck there were enlarged glands. On the left side there was a mass of hard glands extending from the angle of the jaw to the midline. The overlying skin showed a purplish discoloration. There was one small sinus. On the right side there was a similar mass of firm, adherent glands filling the anterior cervical triangle. None of the glands were fluctuant, none were tender. There was a bilateral chain of firm glands in the posterior cervical triangles and in each axilla. The spleen was readily palpable and soft. On percussion the splenic dulness began in the seventh interspace and extended 6 cm. below the left costal margin. There was no increased retromanubrial dulness.

The laboratory data on admission were: Leucocytes 47,700; red cells 3,800,000; hemoglobin 70 per cent.

Differential:

	%
P.M.N.	64.0
P.M.E.	2.5
S.L.	17.0
Trans.	11.0
Myelo.	2.5
L.M.	2.0
L.L.	1.0

With an oxidase stain the differential read:

	%
P.M.N.	71.0
S.L.	13.5
Mono.	13.0
Myelo.	2.5

Vital staining by Dr. Wislocki showed:

	%
P.M.N.	85.0
P.M.E.	2.0
S.L.	6.0
Mono.	5.0
Myelo.	1.0

An x-ray of the chest showed non-tuberculous infiltration at the roots. The sinuses were clear, and an x-ray of the cervical spine showed a large swelling of the soft tissues displacing the esophagus and trachea.

The blood Wassermann was negative. Two milligrams of tuberculin, given intradermally, caused no reaction. Agglutination with Bacillus tularensis was negative. A biopsy was performed and cultures were made of an excised gland. A guinea-pig was inoculated intraperitoneally with infected material from one gland.

Differential diagnosis. The diagnoses suggested for this case were leukemia, Hodgkin's disease, tuberculous adenitis, and non-specific cervical adenitis. The

white blood count, which had been over 50,000 cells per cubic millimeter, suggested leukemia, but careful differential stains made this diagnosis untenable. The complete collar of cervical glands, the splenomegaly, the anemia, the fever, and the general glandular enlargement lent weight to the diagnosis of Hodgkin's disease. To offset this, however, were the coalescence and adherence of the gland masses, and the leucocytosis. The glands felt as if they were tuberculous, but their distribution, the absence of multiple sinuses and fluctuation, the negative tuberculin test, and the leucocytosis ruled out this diagnosis. The gland that was excised for microscopic examination showed a non-specific inflammatory reaction. From the bacteriological cultures Dr. J. Howard Brown grew Bacillus fusiformis. Repeated cultures from the infected glands always yielded the same organism. The guinea-pig inoculated with pus from a gland did not develop tuberculosis.

Course. The size of the masses steadily increased. There was no evidence of fluctuation. After two weeks there was sufficient interference with the lymphatic drainage to cause puffiness of the face. The breathing became increasingly difficult and necessitated a tracheotomy. The patient had such difficulty in swallowing that she refused to eat and had to be gavaged. A week later one of the glands on the left side softened and was incised. Only a few drops of pus were obtained. A similar condition developed on the right side, but no pus was found. After these incisions the condition in the neck became worse. The patient was given a transfusion of 200 c.c. of citrated blood, with only temporary improvement in her hemoglobin. One month after admission the white blood count was 30,000, the red blood count 3,610,000 and the hemoglobin 60 per cent. At this time large doses of potassium iodide were commenced and continued for several weeks without apparent benefit. On two occasions during the fifth and sixth weeks in the hospital a number of glands were suspected of being fluctuant, but the incisions yielded only blood and were followed by increased swelling and induration. It was then decided to refrain from further incisions and to compress the infected areas vigorously. Within two weeks there was noticeable decrease in the size of the glands. Soon thereafter the tracheotomy tube was removed and the gavages were discontinued. One or two glands in the posterior triangles became large and hard, but subsided under the application of the hot compresses. The masses continued to become smaller without suppuration. The induration of the skin and subcutaneous tissues subsided. Ten weeks after admission the patient became afebrile. A week later, on discharge from the hospital, there were still three slightly enlarged glands, a palpable spleen, a leucocytosis of 27,000, and a hemoglobin of 70 per cent. Two months later the glands had entirely subsided, but the white count remained high—18,000. During the nine months that have elapsed there has been no evidence of recurrence.

Comment. As far as we know this is the first report of an adenitis due

to Bacillus fusiformis, although Davis and Pilot[1] repeatedly obtained this organism from the crypts of tonsils and in cases of chronic otitis media. It seems probable that similar infections frequently occur in the cervical glands and are not differentiated from tuberculous adenitis. It was obvious in this case that incision and drainage of the glands caused a regional dissemination of the infection, whereas hot compresses hastened the healing. This case once again raises the question of the advisability of tonsillectomy in children merely on the basis of their having occasional sore throats.

[1] Davis, D. J., and I. Pilot: Collected Studies from the Department of Pathology and Bacteriology, University of Illinois, **6**, 3, 1922–23.

ACETONE BODIES IN NORMAL PREGNANCY AND IN THE TOXEMIAS OF PREGNANCY[1]

H. J. STANDER AND J. F. CADDEN

From the Department of Obstetrics, Johns Hopkins University and Hospital

In a recent publication (1) we have shown that the term "acidosis of pregnancy" is a misnomer, inasmuch as complete acid base studies did not reveal an accumulation of abnormal acids, but instead a reduction in total base, so that normal pregnancy is always associated with a "compensated alkali deficit." It was furthermore shown that eclampsia is often accompanied by a true acidosis or an uncompensated alkali deficit, especially at the time of convulsions.

One of the ways in which the alkali reserve of the blood may be depleted is by an increased production of acetone bodies which are excreted through the kidneys in the form of their salts, most of the base for which comes from the alkali reserve in the blood. In an attempt to understand the etiology of the remarkable reduction in total base observed in all normal pregnancies we have studied the acetone bodies in the blood of a series of normal, non-pregnant and pregnant women, as well as in the several toxemias of pregnancy.

In the oxidation of fats in the human body, the fat is first hydrolyzed to fatty acids and glycerol, the latter then behaving as a glucid. The fatty acid, on the other hand, is desaturated in the liver before oxidation of the unsaturated carbon atoms begins. In the process of oxidation the reaction continues until the last four carbon atoms are reached, and normally these become oxidized as a butyric acid molecule; while under certain abnormal conditions only a partial oxidation occurs. This 4 C atom group (butyric), therefore, seems to represent a residue which is more resistant to oxidation than the rest of the fatty acid molecule. The first step in the oxidation of the butyric acid is probably the formation of B-oxybutyric acid which is then oxidized to acetoacetic (diacetic) acid and then to acetone, although

[1] Submitted for publication October 18, 1930.

it is also claimed that the acetoacetic acid may be formed from the butyric acid by oxidation and the B-oxybutyric acid then formed from the acetoacetic acid by reduction. Whichever may be the case in the human body, we know that glucose in some unknown manner facilitates the breaking up of such ketones as acetoacetic acid, and so performs a ketolytic function. We regard glucose as an antiketogenic substance, or one that prevents the formation of ketone bodies. The antiketogenic substances are represented by the preformed carbohydrate of the food, that part of the protein molecule capable of forming sugar in the body, as well as the glycerin portion of the fat metabolized; while the ketogenic substances, or those which favor ketone formation, are the metabolized fatty acids and that part of the protein molecule which forms tyrosin, leucin and phenylalanin. It is well established that a definite ketogenic-antiketogenic (K/A) ratio is essential in the diet in order to prevent ketosis, which is the formation in the body of the ketoacids,—beta-hydroxybutyric and acetoacetic acids together with smaller amounts of acetone. As early as 1893, Vicarelli (2) noted the presence of acetone bodies in the urine of pregnant women. Porges and Novak (3), as well as Harding (4), have shown that a carbohydrate-low diet leads to acetonuria in normal pregnant women, while an identical diet does not produce acetonuria in a non-pregnant woman. These findings as well as those of Bokelmann and Bock on blood acetone bodies have further stimulated us to carry out the present study.

METHODS

All blood specimens, with the exception of those from eclamptic patients, were obtained in the morning before breakfast or at least three hours after the last meal. Sodium oxalate was used as an anticoagulant. It must be pointed out here that a citrate salt should not be used as an anticoagulant, because, as stated by Clark and Hausman (5), an hydroxy acid on oxidation forms an aldehyde which will give an error in the final acetone figure.

A Folin-Wu filtrate was then prepared from the whole blood and was used for acetone bodies and lactic acid determinations. For the former from 25 to 100 cc. and for the latter 5 cc. of filtrate were used. The acetone determinations were carried out according to the method

of Engfeldt (6), as modified by Bokelmann, Bock and Rother (7); and in the final calculations the factor 0.0986, as given by Folin (8), was employed to transfer the number of cubic centimeters of 0.01 N iodine solution used to milligrams of acetone. All our figures for acetone bodies which include free acetone, acetoacetic acid and B-oxybutyric acid, are recorded as milligrams of acetone per liter of blood.

Lactic acid was determined by the procedure of Friedmann and Kendall (9).

RESULTS

In the study of the blood acetone bodies we found it necessary to know the lactic acid content of our specimens, since the work of

TABLE I

LACTIC ACID SOLUTION, MGS. LACTIC ACID PER 100 CC.	ACETONE EQUIVALENT IN MGS. PER 100 CC.	FACTOR FOR LACTIC ACID TO ACETONE PER LITER
35.8	17.6	0.50
53.8	33.8	0.63
71.6	45.4	0.63
89.6	56.4	0.63
51.0	36.9	0.72
17.0	10.3	0.60
34.0	23.6	0.69
Average		0.63

Smith (10) and van Slyke (11) makes it apparent that the presence of lactic acid interferes with the determination of the total acetone bodies. Although these authors used a different method for the determination of acetone bodies, we thought it advisable to investigate the effect of lactic acid on the method of Engfeldt. Known solutions of lactic acid were analyzed for acetone yield by this method, and the values in Table I show our results. These figures agree with van Slyke's findings that about 110 mgms. of lactic acid per 100 cc. yield a concentration of 1 millimol of acetone bodies per liter of blood; in other words, about 58 mgms. of acetone per liter. We have used the factor 0.59 to express our lactic acid values in equivalent of acetone bodies. We have further checked this factor by adding known

amounts of lactic acid to blood filtrates in which the lactic acid and acetone bodies had previously been determined, and then analyzing for total acetone bodies in the filtrate-lactic acid mixture. In all subsequent tables we express the determined acetone bodies and lactic acid, and then give the corrected acetone bodies, using the above

TABLE II

Non-pregnant women

CASE NUMBER	ACETONE BODIES, MGS. PER 1000 CC. BLOOD	LACTIC ACID, MGS. PER 100 CC. BLOOD	ACETONE BODIES CORRECTED, MGS. PER 1000 CC. BLOOD
1	26.3	16.5	16.8
2	21.8	17.8	11.4
3	29.0	21.6	16.5
4	25.4	14.6	16.9
5	22.6	13.2	15.0
6	26.8	14.9	18.2
Average.....	25.3	16.4	15.8

TABLE III

Normal pregnancy

CASE NUMBER	DURATION OF PREGNANCY	ACETONE BODIES, MGS. PER 1000 CC. BLOOD	LACTIC ACID, MGS. PER 100 CC. BLOOD	ACETONE BODIES CORRECTED, MGS. PER 1000 CC. BLOOD
7	4 months	47.5	41.8	23.5
8	8½ months	36.6		
9	9 months	36.9	42.9	12.0
10	9 months	37.2	34.9	14.1
11	Term	27.9	22.0	15.1
12	Term	27.3	14.9	18.7
13	Term	30.5	34.5	10.5
Average		35.7	33.3	16.6

factor to obtain the lactic acid acetone equivalent. All values for acetone bodies are expressed as milligrams of acetone per liter of blood.

In Table II are shown the findings in six normal non-pregnant women. These average 16.4 mgs. lactic acid per 100 cc. blood and

15.8 mgs. acetone bodies (corrected) per liter of blood, values which are in accordance with the accepted normal non-pregnant values (12). In normal pregnancy (Table III), we see a slight increase in the acetone bodies, as well as a slightly higher lactic acid value than that reported by Stander and Radelet (13).

In low reserve kidney the acetone bodies are slightly elevated (Table IV), but unfortunately we have studied only two patients

TABLE IV

Low reserve kidney

CASE NUMBER	DURATION OF PREGNANCY	ACETONE BODIES, MGS. PER 1000 CC. BLOOD	LACTIC ACID, MGS. PER 100 CC. BLOOD	ACETONE BODIES CORRECTED, MGS. PER 1000 CC. BLOOD
14	Term	38.7	18.7	27.9
15	1 day P.P.	41.6	16.4	32.1
Average		40.2	17.6	30.0

TABLE V

Nephritis complicating pregnancy

CASE NUMBER	DURATION OF PREGNANCY	ACETONE BODIES, MGS. PER 1000 CC. BLOOD	LACTIC ACID, MGS. PER 100 CC. BLOOD	ACETONE BODIES CORRECTED, MGS. PER 1000 CC. BLOOD
16	Term	27.7	32.9	8.6
17	Term	27.5	15.8	18.3
18	Term 1 day A.P.	62.7	23.9	48.8
19	1 day P.P.	56.5	22.5	43.5
Average		43.6	23.7	29.8

suffering from this type of toxemia. In nephritis the acetone bodies in the blood may be normal, although in two of our four cases we observed an increase above the normal values. Accordingly, the average for nephritis complicating pregnancy is above the upper limit of normal.

In eclampsia the findings are interesting and significant. As shown before by several authors, lactic acid is definitely increased, but even

after correcting for its marked elevation we note a decided rise in the blood acetone bodies, the average being 50.2 mgs. per liter of blood.

TABLE VI

Eclampsia

CASE NUMBER	ACETONE BODIES, MGS. PER 1000 CC. BLOOD	LACTIC ACID, MGS. PER 100 CC. BLOOD	ACETONE BODIES CORRECTED, MGS. PER 1000 CC. BLOOD	BLOOD SPECIMENS OBTAINED
20	78.7			8 minutes after 6th convulsion
	83.2			Immediately after 8th convulsion
	64.8			12 hours after delivery and 14 hours after 20th convulsion. Patient semi-conscious
21	78.0			40 minutes after 2nd, immediately after 3rd convulsion
22	44.3			33 minutes after 4th convulsion
	52.7			25 minutes after 6th convulsion
23	54.7	29.3	37.7	40 minutes after 7th convulsion
24	103.3	13.5	95.5	8 hours after convulsion
	27.9			12 days after last convulsion and 12 days after delivery
25	84.1	50.9	54.6	1 hour after convulsion
26	78.3	84.0	32.0	5 minutes after 3rd convulsion
	75.9	77.0	31.2	Immediately after 6th convulsion
	27.3	19.0	16.3	18 hours after delivery last convulsion, and improved
Average..	72.6	50.9	50.2	During period of convulsion

DISCUSSION

We have reported all our values for acetone bodies (free acetone, diacetic acid, and B-oxybutyric acid) as acetone, while Bokelmann and his coworkers have expressed their results in diacetic acid, which means that their figures should be almost twice as high as ours, or in the ratio of 102 to 58. Nevertheless, we have observed changes in the

different toxemias of pregnancy similar to those reported by them, although our absolute values run somewhat higher. A comparison of our respective results is as follows:

TYPE OF CASE	BOKELMANN, BOCK AND ROTHER		STANDER AND CADDEN	
	Uncorrected as diacetic	Uncorrected as acetone	Uncorrected as acetone	Corrected as acetone
Non-pregnant	29.85	16.5	25.3	15.8
Pregnancy	39.48	22.5	35.7	16.6
Nephritis	75.41	42.9	43.6	29.8
Eclampsia	106.73	60.7	72.6	50.2

Our findings show that the toxemias of pregnancy, low reserve kidney and nephritis complicating pregnancy, are associated with a tendency toward an accumulation of acetone bodies in the blood, while in eclampsia there is a definite hyper-acetonemia which probably helps in the production of the uncompensated alkali deficit so often seen immediately after a convulsion. Our figures do not reveal a hyper-acetonemia in normal pregnancy, although both our uncorrected and corrected acetone values are above the average for normal non-pregnant women.

It seems that a disturbance in the oxidation of fatty acids may take place more readily in pregnant than in normal non-pregnant women, with the production of ketone substances. This may in part explain the lowered alkali reserve in the blood of pregnant women, as outlined in the earlier part of this paper. A decrease in maternal carbohydrate, resulting from a drain on it by the foetus, or a change in the maternal fat metabolism, may be the cause of the ketosis. Schmidt and Wingen (14) suggest that the increased carbohydrate requirement in pregnancy is met partly by fat being converted into glycogen in the liver, and that during this transformation acid by-products (ketones) may appear, which will deplete the alkali reserve of the mother's blood. Bokelmann and Bock (15) demonstrated definitely a greater tendency toward ketosis in normal pregnancy.

From this discussion it appears probable that we may help the metabolism of pregnant women by decreasing fat and increasing carbohydrate in their diet. It is interesting to recall here the original

work of Duncan and Harding (16) upon the value of a high carbohydrate diet in the vomiting of pregnancy, and we hope shortly to be able to publish blood acetone values in the various stages of that condition, more particularly as Bokelmann and Bock have reported a marked increase in acetone bodies in the blood of women suffering from it.

CONCLUSIONS

1. The total acetone bodies (free acetone, acetoacetic acid and B-oxybutyric acid) in the blood in normal non-pregnant women vary between 11 and 18 mgs. acetone per liter of blood, after correction for lactic acid, the average being 15.8 mgs.

2. In normal pregnancy the total corrected acetone bodies vary between 11 and 24 mgs. per liter of blood, with an average slightly higher than in the non-pregnant woman (16.6 mgs.).

3. The total corrected acetone bodies in the blood of pregnant women with nephritis lies between 8.6 and 48.8 mgs. acetone per liter of blood.

4. Eclampsia is accompanied by a definite elevation in the quantity of acetone bodies in the blood, averaging 50.2 mgs. acetone per liter of blood.

5. The tendency toward ketosis in pregnant women may in part explain the lowered total base observed in their blood as term is approached.

6. The increased acetone bodies in the blood of eclamptic patients may be a partial factor in producing the uncompensated alkali deficit seen in that disease, although lactic acid accumulation is perhaps the major factor in the causation of this acidosis.

7. A diet low in fats and high in carbohydrates seems indicated in normal pregnancy, and must certainly be of value in the cases of toxemias showing evidence of ketosis.

BIBLIOGRAPHY

(1) Stander, H. J., Eastman, N. J., Harrison, E. P. H., and J. F. Cadden: *Jour. Biol. Chem.*, 1929, lxxxv, 233.
(2) Vicarelli: *Prager Med. Wchnschr.*, 1893, xvi, 8.
(3) Novak, J., and O. Porges: *Berl. klin. Wchnschr.*, 1911, xlviii, 1757.
(4) Harding, V. J.: *Lancet*, 1921, ii, 327.
(5) Clark, B. E., and G. H. Hausman: *Arch. Path.*, 1928, vi, 881.

(6) ENGFELDT, N. O.: *Biochem. Ztschr.*, 1924, cxliv, 556.
(7) BOKELMANN, O., BOCK, A., AND J. ROTHER: *Ztschr. f. Geburtsh. u. Gynäk.*, 1926, lxxxix, 1.
(8) FOLIN, O.: Laboratory Manual of Biochemistry, New York, 1926.
(9) FRIEDMANN, T. E., AND A. I. KENDALL: *Jour. Biol. Chem.*, 1929, lxxxii, 23.
(10) SMITH, E. C.: *Biochem. Jour.*, 1926, xx, 1024.
(11) VAN SLYKE, D. D.: *Jour. Biol. Chem.*, 1929, lxxxiii, 415.
(12) CLAUSEN, S. W.: *Ibid.*, 1922, lii, 263.
(13) STANDER, H. J., AND A. H. RADELET: *Johns Hopkins Hosp. Bull.*, 1926, xxxix, 91.
(14) SCHMIDT, H. R., AND T. WINGEN: *Arch. f. Gynäk.*, 1928, cxxxiii, 127.
(15) BOKELMANN, O., AND A. BOCK: *Klin. Wchnschr.*, 1927, vi, 549.
(16) DUNCAN, J. W., AND V. J. HARDING: *Can. Med. Assn. Jour.*, 1918, viii, 1057.

PROGRAMS OF THE MEDICAL RESEARCH SOCIETY
1929–1930

NOVEMBER 1ST, 1929

Changes in the plasma electrolyte content during fever. Rustin McIntosh.
Anaerobic fertilization. E. G. Barron.

DECEMBER 6TH, 1929

The effect of copper on the utilization of iron in haemoglobin regeneration. Hugh Josephs.
The relation of allergy to symptoms in bacterial infections. Lay Martin.

JANUARY 24TH, 1930

The lactic acid content of the heart in hyperthyroidism. E. C. Andrus.
The anaerobic flora of the nose. Perrin Long.

FEBRUARY 14TH, 1930

The demonstration that the occurrence of acute yellow atrophy during salvarsan treatment can be prevented by diet. Dr. Craven (Introduced by Arnold Rich).
Studies on guanidine. Read Ellsworth.
Experiments on the cause of cataract. Jonas Friedenwald.

MARCH 28TH 1930

A study of the effectiveness of ultraviolet therapy in several diseases. Henry S. Willis.
The demonstration that allergic inflammation is not necessary for the operation of immunity in pneumococcal infections. Arnold Rich and J. Howard Brown.
The reduction potential of sugars, and its biological significance. E. G. Barron.

APRIL 25TH, 1930

Studies on natural immunity to the gonococcus. David M. Davis.
A study of the relation of yaws to syphilis. J. B. Turner.
The insulin content of the human diabetic pancreas. Frank Kindell.

MAY 26TH, 1930

The relation of the exact sciences to medical practice and research. Wm. A. Perlzweig.

The importance of the study of the pathological physiology of single calls. E. G. Barron.

Problems involved in the guidance of beginners in medical research. Bengt Hamilton.

INDEX TO VOLUME XLVII

Acetone bodies in normal pregnancy and in the toxemias of pregnancy 382
Allergy, Observations on the relation of, to immunity 189
Amyotonia congenita (Oppenheim's Disease) in identical twins 309
Arteries, superficial cerebral, On the origin of miliary aneurysms of the 239

Bacillus fusiformis, Cervical adenitis due to 378
Baker, B. M., Jr., and Donald McEachern, The effect of the ingestion of potassium iodide on the electrocardiogram of normal individuals 304
Blood guanidine base concentration in normal individuals and in patients with liver injury, Response of, to the ingestion of methyl guanidine sulphate 106
Book Reviews and Books Received 231
Bordley, James, III, Disappearance of diabetes mellitus during the development of cirrhosis of the liver 113

Cadden, J. F., and H. J. Stander, Acetone bodies in normal pregnancy and in the toxemias of pregnancy 382
Circulation, hepatic and portal, On the manner of anastomosis of the 176
Deliveries, forceps, Practical conclusions drawn from one thousand 382
Diabetes mellitus, Disappearance of, during the development of cirrhosis of the liver .. 113

Eagle, Harry, An explanation of the mechanism of the Wassermann and precipitation tests for syphilis 292
Eastman, Nicholson J., Foetal blood studies. I. The oxygen relationships of umbilical cord blood at birth 221
Ellsworth, Read McLane, Response of blood guanidine base concentration in normal individuals and in patients with liver injury to the ingestion of methyl guanidine sulphate 106
Encephalitis, epidemic, The prognosis for, in children 123

Firor, W. M., Cervical adenitis due to bacillus fusiformis 378
Foetal blood studies. I. The oxygen relationships of umbilical cord blood at birth 221
Forbus, Wiley D., On the origin of miliary aneurysms of the superficial cerebral arteries 239
Forbus, Wiley D., and Fred S. Wolf, Amyotonia congenita (Oppenheim's Disease) in identical twins 309
Frobisher, Martin Jr., and Isabelle Gilbert, The hydrolysis of sodium hippurate by various bacteria 55

Gilbert, Isabelle, and Martin Frobisher, Jr., The hydrolysis of sodium hippurate by various bacteria 55
Glomeruli, The number and size of the, in the kidney of several mammals 285
Guttmacher, Manfred S., The views of Adam Smith on medical education 164

Hamilton, Bengt, Laslo Kajdi and Dorothy Meeker, The relation between phosphorus, chloride and bicarbonate in the serum of rachitic and normal rabbits..... 215
Heliotherapy, Experiences with artificial..... 186
Howe, H. A., The prognosis for epidemic encephalitis in children..... 123

Jaundice, The pathogenesis of the forms of..... 338

Kajdi, Laslo, Rustin McIntosh and Dorothy Meeker, The response of plasma water and electrolytes to elevation of body temperature..... 61
Kajdi, Laslo, Bengt Hamilton and Dorothy Meeker, The relation between phosphorus, chloride and bicarbonate in the serum of rachitic and normal rabbits..... 215
King, John T., Jr., and Walter K. Myers, Observations on the menopause. III. Sensitiveness of women at the menopause to epinephrine..... 22
Kunkel, P. A., Jr., The number and size of the glomeruli in the kidney of several mammals..... 285

Langworthy, Orthello R., Histological changes in nerve cells following injury..... 11

McEachern, Donald, The effect of potassium iodide on the pulse rates of normal individuals..... 299
McEachern, Donald, and B. M. Baker, Jr., The effect of the ingestion of potassium iodide on the electrocardiogram of normal individuals..... 304
McIntosh, Rustin, Laslo Kajdi and Dorothy Meeker, The response of plasma water and electrolytes to elevation of body temperature..... 61
Meeker, Dorothy, Rustin McIntosh and Laslo Kajdi, The response of plasma water and electrolytes to elevation of body temperature..... 61
Meeker, Dorothy, Bengt Hamilton and Laslo Kajdi, The relation between phosphorus, chloride and bicarbonate in the serum of rachitic and normal rabbits..... 215
Menopause, Observations on the, III. Sensitiveness of women at the menopause to epinephrine..... 22
Myers, Walter K., and John T. King, Jr., Observations on the menopause, III. Sensitiveness of women at the menopause to epinephrine..... 22

Nerve Cells, Histological changes in, following injury..... 11

Olds, John McKee, and Edward Stephens Stafford, On the manner of anastomosis of the hepatic and portal circulations..... 176

Phosphorus, chloride and bicarbonate, The relation between, in the serum of rachitic and normal rabbits..... 215
Placenta, Observations on the, from a case of malaria..... 157
Plasma Water and electrolytes, The response of, to elevation of body temperature.. 61
Potassium iodide, The effect of, on the pulse rates of normal individuals..... 299
Potassium iodide, The effect of the ingestion of, on the electrocardiogram of normal individuals..... 304

Rich, Arnold Rice, Observations on the relation of allergy to immunity..... 189
Rich, Arnold Rice, The pathogenesis of the forms of jaundice..... 338

Smith, Adam, The views of, on medical education 164
Sodium hippurate, The hydrolysis of, by various bacteria 55
Stafford, Edward Stephens, and John McKee Olds, On the manner of anastomosis of the hepatic and portal circulations 176
Stander, H. J., Practical conclusions drawn from one thousand forceps deliveries ... 382
Stander, H. J., and J. F. Cadden, Acetone bodies in normal pregnancy and in the toxemias of pregnancy 382
Syphilis, Tests for, An explanation of the mechanism of the Wassermann and precipitation reactions 292

Thomas, Henry M., Jr., Thyroid heart, a transitory condition 1
Thyroid Heart, a transitory condition 1

Willis, Henry Stuart, Experiences with artificial heliotherapy 186
Wilmer Institute, Dedication of 44
Wislocki, George B., Observations on the placenta from a case of malaria 157
Wolf, Fred S., and Wiley D. Forbus, Amyotonia congenita (Oppenheim's Disease) in identical twins 309

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, E. Cowles Andrus

EDITORIAL BOARD

Edward P. Carter
Charles R. Austrian
Arnold R. Rich
Paul G. Shipley
Frank R. Smith
George B. Wislocki

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of the Johns Hopkins Hospital, Baltimore, Md.

Books for review should be sent to The Editor at the above address.

Twenty-five reprints, with covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Johns Hopkins Press, Baltimore, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of the current volume be out of print at the time the subscription order is received, the pro rata value of such numbers will be credited to the next volume, and the renewal invoice therefore adjusted accordingly.

Subscriptions should be renewed promptly—To avoid a break in your series, subscriptions should be renewed promptly. The publishers cannot guarantee to supply back issues on belated renewals.

Subscriptions, new or renewal, may be sent to the Publishers or ordered through your agent.

Agents for the British Empire, except Canada: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, W.C. 2, London.

THE JOHNS HOPKINS PRESS

BALTIMORE, MARYLAND, U. S. A.

AT THE MENOPAUSE

The distressing symptoms that so often accompany the climacteric, but more particularly the aggravated symptoms of the artificial menopause, are frequently controlled by the administration of

LUTEIN TABLETS, H. W. & D.
LUTEIN SOLUTION AMPULES, H. W. & D.

The choice of the medication depends, of course, on the judgment of the physician as to whether oral or hypodermatic administration is indicated. Both products represent the

CORPUS LUTEUM OF THE SOW

Lutein Tablets H. W. & D. are unmodified by treatment with solvents or by exposure to temperatures above animal body heat in the drying process. All separation of extraneous matter is made by mechanical means and all drying is *in vacuo*. The unaltered *corpus luteum* should, therefore, be presented in our products and clinical experience with them should demonstrate their therapeutic activity.

Ovarian dysfunction as evidenced in dysmenorrhea and amenorrhea is also an indication for Lutein medication. Where the diagnosis of such dysfunction was well established, definite therapeutic results have been reported.

WHOLE OVARY TABLETS, H. W. & D.
OVARIAN RESIDUE TABLETS, H. W. & D.

are also offered for those who prefer, for certain indications, the use of the whole gland or of the residue remaining after corpus luteum separation.

Literature furnished on request

H. W. & D.—SPECIFY—H. W. & D.—SPECIFY—H. W. & D.—SPECIFY—H. W. & D.

HYNSON, WESTCOTT & DUNNING : : Baltimore, Md.

A BRIEF

For Insulin

Its proper use in diabetes . . .

- Restores muscle strength
- Renews mental acumen
- Brings body weight to near normal
- Permits continued pursuit of gainful occupation, and maintenance of economic independence
- Increases resistance to infections
- Reduces danger of surgical operation
- Decreases death rate from diabetic coma
- Prolongs life

For Insulin, Mulford

- Manufactured under license from the University of Toronto
- Carefully standardized by elaborate biological assay methods
- Highly purified, practically colorless, and stable
- Notably free from reaction-producing proteins
- Very low nitrogen content
- Practically no sting when injected
- Filled and packed in convenient containers

In 5 cc and 10 cc containers

10, 20, 40 and 80-unit strengths per cc

H. K. MULFORD COMPANY, PHILADELPHIA